Post Approval Submissions

Modification Information

To modify an approved study, edit the individual answers that make up the application. The questions below are intended solely for the IRB to have a summary statement of your requested action. The modifications cannot be processed until the actual changes have been made throughout the application.

1. Provide a brief non-technical summary of any changes you will be making to the study (i.e., study application, project personnel, and/or study documents.) The text you enter here will be reproduced in the IRB approval document, and should contain the details that you and/or your sponsor find relevant (e.g., master protocol/amendment version number and date). Typical summaries are 50-100 words. PLEASE NOTE: THIS SECTION MAY BE EDITED BY THE IRB FOR CLARITY OR LENGTH.

   This modification is to request the personnel change,

   Add William Wu to the protocol and remove Joseph DelFerro, Elise Hickman, and Mathew Meyer.

2. Is this study in Data Analysis only (i.e. enrollment, intervention and follow-up are complete)?

   No

Total number of subjects enrolled to date:

25

Is this study currently open to the enrollment of new subjects?

Yes

Total number of subjects actively participating (i.e., Total number of subjects involved in the interventional part of this study. If the study is limited to data collection (e.g., surveys, questionnaires, collection of data from existing records), enter '0':

4

3. Do you have plans to re-consent subjects as a result of this modification?

   No

4. Is this modification being submitted in response to New Safety Information?

   No

5. Have the risks as described in A.6., consent form, or any other study document changed? This may include new risks not previously listed, changes in frequency of known risks, or removal of previously listed risks.

   No

Continuing with Modifications

Click the "save and continue" button to access your existing application.
You may make any changes to the application that you are requesting at this time.

General Information

1. General Information

1. Project Title

   Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects

2. **Brief Summary**. Provide a **brief non-technical description** of the study, which will be used in IRB documentation as a description of the study. Typical summaries are 50-100 words. Please reply to each item below, retaining the subheading labels already in place, so that reviewers can readily identify the content. PLEASE NOTE: THIS SECTION MAY BE EDITED BY THE IRB FOR CLARITY OR LENGTH.

   Purpose: A growing body of epidemiological data suggests an increased risk of cardiovascular events associated with air pollution. One of the common air pollutants, ozone, has been shown to induce oxidative

stress and inflammation in the cardiovascular and respiratory systems. This proposed study is to examine the efficacy of fish oil and olive oil in modulating cardiovascular and pulmonary functions after ozone exposure. The objective is to understand the mechanistic basis for the health effects of ozone relative to those air pollutants. Treatment groups will include forty healthy young adults who will be given dietary supplementation of fish oil or olive oil. A control group will consist of 20 healthy volunteers who will receive no supplements. After 4 weeks, subjects will be exposed to clean air for 2 hours on the first day, then ozone for 2 hours on the second day. Cardiac rhythm, pulmonary function, vascular responses, endothelial function, and markers of coagulation and airway inflammation pre- and post- ozone exposure will be measured. This study is designed to build on the previous nutritional supplement interventional studies OMEGACON (IRB # 07-0190) and CAPTAIN (IRB # 11-1807), in order to understand the mechanism of action of particulate pollutants in comparison to that of ozone, a known oxidant air contaminant.

Participants: A total of sixty healthy 18-35 year-old male and female subjects will be involved in the study.

Procedures (methods): Forty healthy young adults will receive dietary supplementation consisting of fish oil or olive oil for 4 weeks. The control group includes 20 healthy volunteers who will receive no supplements in the study. After 4 weeks of supplementation or control regiment, each subject will be exposed to clean air for 2 hours on the first day, then ozone for 2 hours on the second day.

2. Project Personnel

1. Will this project be led by a STUDENT (undergraduate, graduate) or TRAINEE (resident, fellow, postdoc), working in fulfillment of requirements for a University course, program or fellowship?

   No

2. List all project personnel beginning with principal investigator, followed by faculty advisor, co-investigators, study coordinators, and anyone else who has contact with subjects or identifiable data from subjects.

   - List ONLY those personnel for whom this IRB will be responsible; do NOT include collaborators who will remain under the oversight of another IRB **for this study**.
   - If this is Community Based Participatory Research (CBPR) or you are otherwise working with community partners (who are not functioning as researchers), you may not be required to list them here as project personnel; consult with your IRB.
   - If your extended research team includes multiple individuals with limited roles, you may not be required to list them here as project personnel; consult with your IRB.

   The table below will access campus directory information; if you do not find your name, your directory listing may need to be updated.
   If a change to the Principal Investigator is requested during the course of the study, a PI Change Form must be submitted.

University of North Carolina at Chapel Hill (UNC-CH)

Full Name	Role	IRB Training	GCP COI Number	Initial COI Disclosure	Potential Conflict	COI Review Process	COI Review Result
James Samet	Principal Investigator	✓	✗ 19-18273	✓		Completed	No Conflict
Neil Alexis	Co-investigator	✓	✓ 19-18280	✓		Completed	No Conflict
Haiyan Tong	Co-investigator	✓	✗ 19-18272	✓		Completed	No Conflict
Martin Case	Study Coordinator	✓	✗ 19-18276	✓		Completed	No Conflict
Claudia Salazar	Study Coordinator	✓	✗ 19-18282	✓		Completed	No Conflict
Hao Chen	Research Assistant	✓	✗ n/a	n/a			n/a
Katherine Mills	Research Assistant	✓	✓ n/a	n/a			n/a
Brian Ring	Research Assistant	✓	✓ n/a	n/a			n/a
Martha Almond	Other	✓	✓ n/a	n/a			n/a
Philip Bromberg	Other	✓	✓ 19-18275	✓		Completed	No Conflict

Melissa Caughey	Other	✓	✓ 19-18277	✓		Completed	No Conflict
Elizabeth Corteselli	Other	✓	✗ n/a	n/a			n/a
Robert Devlin	Other	✓	✗ 19-18274	✓		Completed	No Conflict
Radhika Dhingra	Other	✓	✓ 19-18283	✓		Completed	No Conflict
David Diaz-sanchez	Other	✓	✗ n/a	n/a			n/a
Andrew Ghio	Other	✓	✗ 19-18278	✓		Completed	No Conflict
Alan Hinderliter	Other	✓	✓ 19-18279	✓		Completed	No Conflict
Sally Ivins	Other	✓	✓ n/a	n/a			n/a
Syed Masood	Other Student	✓	✗ n/a	n/a			n/a
Tracey Montilla	Other	✓	✓ n/a	n/a			n/a
David Peden	Other	✓	✓ 19-18281	✓		Completed	No Conflict
Ana Rappold	Other	✓	✗ n/a	n/a			n/a
Carole Robinette	Other	✓	✓ n/a	n/a			n/a
Julie Wood	Other	✓	✗ n/a	n/a			n/a
William Wu	Other Student volunteer	✓	✗ n/a	n/a			n/a

NOTE: The IRB database will link automatically to UNC Human Research Ethics Training database and the UNC Conflict of Interest (COI) database. Once the study is certified by the PI, all personnel listed (for whom we have email addresses) will receive separate instructions about COI disclosures. The IRB will communicate with the personnel listed above or the PI if further documentation is required.

3. If this research is based in a center, institute, or department (Administering Department) other than the one listed above for the PI, select here. Be aware that if you do not enter anything here, the PI's home department will be AUTOMATICALLY inserted when you save this page.

Department	Aux Services Affiliates: EPA

3. Funding Sources

1. Is this project funded (or proposed to be funded) by a contract or grant from an organization EXTERNAL to UNC-Chapel Hill?

Yes

Is UNC-CH the **direct** recipient of any Federal funding for this study? You should answer 'yes' *only* if you are the grantee. You should answer 'no' if you are the recipient of a sub-award or contractor under the grant.

No

Funding Source(s) and/or Sponsor(s)

Sponsor Name	UNC Ramses Number	Sponsor Type	Prime Sponsor Name	Prime Sponsor Type	Sponsor/Grant Number	Detail
United States Environmental Protection Agency (EPA)	Currently Not Available	Federal			Intramural fundng within the US EPA	view

2. Is this study funded by UNC-CH (e.g., department funds, internal pilot grants, trust accounts)?
   No

3. Is this research classified (e.g. requires governmental security clearance)?
   No

4. Is there a master protocol, grant application, or other proposal supporting this submission (check all that apply)?

✗ Grant Application
✗ Industry/Federal Sponsor Master Protocol
✗ Student Dissertation or Thesis Proposal
✗ Investigator Initiated Master Protocol
✓ Other Study Protocol

4. Screening Questions

The following questions will help you determine if your project will require IRB review and approval.

The first question is whether this is RESEARCH (click for details)

1. Does your project involve a systematic investigation, including research development, testing and evaluation, which is designed to develop or contribute to generalizable knowledge? PLEASE NOTE: You should only answer yes if your activity meets all the above.
   Yes

The next questions will determine if there are HUMAN SUBJECTS (click for details)

2. Will you be obtaining information or biospecimens through intervention or interaction with the individual, and use, study, or analysis of the information or biospecimens? This would include any communication or interpersonal contact between investigator and subject such as using in-person or online questionnaires/surveys, interviews, focus groups, observations, treatment interventions, etc. PLEASE NOTE: Merely obtaining information FROM an individual does not mean you should answer 'Yes,' unless the information is also ABOUT them.
   Yes

3. Will you be obtaining, using, studying, analyzing, or generating identifiable private information or identifiable biospecimens collected through means other than direct interaction? This would include data, records or biological specimens that are currently existing or will be collected in the future for purposes other than this proposed research (e.g., medical records, ongoing collection of specimens for a tissue repository).
   OR
   Will you be using human specimens that are not individually identifiable for FDA-regulated in vitro diagnostic (IVD) device investigations?
   Yes

The following questions will help build the remainder of your application.

4. Will subjects be studied in the Clinical and Translational Research Center (CTRC, previously known as the GCRC) or is the CTRC involved in any other way with the study? (If yes, this application will be reviewed by the CTRC and additional data will be collected.)
   No

5. Does this study directly recruit participants through the UNC Health Care clinical settings for cancer patients **or** does this study have a focus on cancer or a focus on a risk factor for cancer (e.g. increased physical activity to reduce colon cancer incidence) **or** does this study receive funding from a cancer agency, foundation, or other cancer related group? (If yes, this application may require additional review by the Oncology Protocol Review Committee.)
   No

6. Are any personnel, organizations, entities, facilities or locations in addition to UNC-Chapel Hill involved in this research (e.g., is this a multi-site study or does it otherwise involve locations outside UNC-CH, including foreign locations)? You should also click "Yes" if you are requesting reliance on an external IRB, or that UNC's IRB cover another site or individual. See guidance.

No

Exemptions

Request Exemption

Some research involving human subjects may be eligible for an exemption which would result in fewer application and review requirements. This would not apply in a study that involves drugs or devices, involves greater than minimal risk, or involves medical procedures or deception or minors, except in limited circumstances.

1. Would you like your application evaluated for a possible exemption?

No

Part A. Questions Common to All Studies

A.1. Background and Rationale

A.1.1. Provide a summary of the background and rationale for this study (i.e., why is the study needed?). If a complete background and literature review are in an accompanying grant application or other type of proposal, only provide a brief summary here. If there is no proposal, provide a more extensive background and literature review, including references.

Exposure to air pollution, including particulate matter and ozone (O_3), is a well-known risk factor for respiratory/cardiovascular morbidity and mortality worldwide (reviewed in 1-4). A number of controlled clinical exposure studies have established that ozone exposure induces respiratory oxidative and inflammatory responses, and pulmonary function decrements in children, adults, and elderly populations under resting or exercise status (reviewed in 8). For instance, epidemiological studies have shown that elevated outdoor ozone concentration was significantly correlated with asthma-related emergency department visits among children and the elderly (5-7). However, less attention has been given to cardiovascular responses to ozone exposure. Two recent clinical studies found that exposure to ozone (300 ppb for 2 hr) increases markers of systemic inflammation and adversely affects vascular coagulation and heart rhythm in healthy young volunteers (9-10).

It has also been consistently shown that dietary fish oil (11-14, reviewed in 15) and olive oil (16-18, reviewed in 15 and 19) have anti-oxidant and anti-inflammatory properties when taken as dietary supplements, and effectively protect the cardiovascular system. Our lab has previously (IRB#11-1807 and 07-0190) demonstrated that supplementation with 3 g/d fish oil (20) or olive oil (21) for 28 days attenuated concentrated ambient particulate matter (mean 253±16 µg/m3, 2 hr) -induced heart rate variability changes or endothelial dysfunction, respectively, in healthy middle-aged adults. Interestingly, polyunsaturated fatty acids, such as the omega-3 fatty acids, have been proposed as the primary target for ozone (22). Ozone reacts with the unsaturated C-C double bonds generating free radicals. This process could damage airway lining and the phospholipid components of the cell membranes. The present study is aimed at improving our mechanistic understanding of the toxicology of air pollution by extending this interventional strategy to investigate the role of dietary fatty acids in modulating ozone-induced effects in healthy volunteers.

In this study, we will supplement healthy young adults with fish oil or olive oil for 4 weeks. The control group will receive no supplements during that 4 weeks period. Their cardiac rhythm, pulmonary function, vascular responses, endothelial function, and markers of coagulation and airway inflammation pre- and post- air or ozone exposure will be measured. We hypothesize that air pollutants such as ozone and particulate matter share a common mechanism of action and that, therefore, supplementation with fish oil or olive oil will alter ozone induced cardiac dysrhythmia, pulmonary function decrements, vascular dysfunction, and airway inflammation. The study is designed to build on the previous nutritional supplement interventions studies OMEGACON (IRB # 07-0190) and CAPTAIN (IRB # 11-1807), in order to understand the mechanism of action of particulate pollutants in comparison to that of ozone, a known oxidant air contaminant.

Reference

1. Chin MT. Basic mechanisms for adverse cardiovascular events associated with air pollution. Heart. 2015 Feb;101(4):253-6. doi: 10.1136/heartjnl-2014-306379. Epub 2014 Dec 31.

2. Nasser Z, Salameh P, Nasser W, Abou Abbas L, Elias E, Leveque A. Outdoor particulate matter (PM) and associated cardiovascular diseases in the Middle East. Int J Occup Med Environ Health. 2015;28(4):641-61. doi: 10.13075/ijomeh.1896.00186.

3. Wang C, Tu Y, Yu Z, Lu R. PM2.5 and Cardiovascular Diseases in the Elderly: An Overview. Int J Environ Res Public Health. 2015 Jul 16;12(7):8187-97. doi: 10.3390/ijerph120708187.

4. Kelly FJ, Fussell JC. Linking ambient particulate matter pollution effects with oxidative biology and immune responses. Ann N Y Acad Sci. 2015 Mar;1340:84-94. doi: 10.1111/nyas.12720. Epub 2015 Feb 25.

5. Babin SM, Burkom HS, Holtry RS, Tabernero NR, Stokes LD, Davies-Cole JO, DeHaan K, Lee DH. Pediatric patient asthma-related emergency department visits and admissions in Washington, DC, from 2001-2004, and associations with air quality, socio-economic status and age group. Environ Health. 2007 Mar 21;6:9.

6. Halonen JI, Lanki T, Tiittanen P, Niemi JV, Loh M, Pekkanen J. Ozone and cause-specific cardiorespiratory morbidity and mortality. J Epidemiol Community Health. 2010 Sep;64(9):814-20. doi: 10.1136/jech.2009.087106. Epub 2009 Oct 23.

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10. Kahle JJ, Neas LM, Devlin RB, Case MW, Schmitt MT, Madden MC, Diaz-Sanchez D. Interaction effects of temperature and ozone on lung function and markers of systemic inflammation, coagulation, and fibrinolysis: a crossover study of healthy young volunteers. Environ Health Perspect. 2015 Apr;123(4):310-6. doi: 10.1289/ehp.1307986. Epub 2014 Dec 16.

11. Holguin F, Téllez-Rojo MM, Lazo M, Mannino D, Schwartz J, Hernández M, Romieu I. Cardiac autonomic changes associated with fish oil vs soy oil supplementation in the elderly. Chest. 2005 Apr;127(4):1102-7.

12. Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival--4. Cardiovasc Drugs Ther. 1997 Jul;11(3):485-91.

13. Harris WS. n-3 fatty acids and serum lipoproteins: human studies. Am J Clin Nutr. 1997 May;65(5 Suppl):1645S-1654S.

14. Endres S, von Schacky C. n-3 polyunsaturated fatty acids and human cytokine synthesis. Curr Opin Lipidol. 1996 Feb;7(1):48-52.

15. Moreno JJ, Mitjavila MT. The degree of unsaturation of dietary fatty acids and the development of atherosclerosis. J Nutr Biochem. 2003 Apr;14(4):182-95.

16. Moreno JA, López-Miranda J, Gómez P, Benkhalti F, El Boustani ES, Pérez-Jiménez F. Effect of phenolic compounds of virgin olive oil on LDL oxidation resistance. Med Clin (Barc). 2003 Feb 8;120(4):128-31.

17. Moreno-Luna R, Munoz-Hernandez R, Miranda ML, Costa AF, Jimenez-Jimenez L, Vallejo-Vaz AJ, et al. 2012. Olive oil polyphenols decrease blood pressure and improve endothelial function in young women with mild hypertension. Am J Hypertens. 25:1299-1304.

18. Buckland G, Gonzalez CA. The role of olive oil in disease prevention: a focus on the recent

epidemiological evidence from cohort studies and dietary intervention trials. Br J Nutr. 2015 Apr;113 Suppl 2:S94-101. doi: 10.1017/S0007114514003936.

19. Schwingshackl L, Christoph M, Hoffmann G. Effects of Olive Oil on Markers of Inflammation and Endothelial Function-A Systematic Review and Meta-Analysis. Nutrients. 2015 Sep 11;7(9):7651-75. doi: 10.3390/nu7095356.

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21. Tong H, Rappold AG, Caughey M, Hinderliter AL, Bassett M, Montilla T, Case MW, Berntsen J, Bromberg PA, Cascio WE, Diaz-Sanchez D, Devlin RB, Samet JM. Dietary Supplementation with Olive Oil or Fish Oil and Vascular Effects of Concentrated Ambient Particulate Matter Exposure in Human Volunteers. Environ Health Perspect. 2015 May 1.

22. Kelly FJ, Mudway I, Krishna MT, Holgate ST. The free radical basis of air pollution: focus on ozone. Respir Med. 1995 Nov;89(10):647-56.

A.1.2. State the research question(s) (i.e., specific study aims and/or hypotheses).

This present study is aimed at improving our mechanistic understanding of the toxicology of air pollution by extending this interventional strategy to investigate the role of dietary fatty acids in modulating ozone-induced effects in healthy volunteers.

Hypothesis: Air pollutants such as ozone and particulate matter share a common mechanism of action and supplementation with fish oil or olive oil will change ozone induced cardiac dysrhythmia, pulmonary function decrements, vascular dysfunction, and airway inflammation.

The FDA has reviewed the use of fish oil and olive oil with the study protocol, and given approval to proceed.

A.2. Subjects

A.2.1. Total number of subjects proposed across all sites by all investigators (provide exact number; if unlimited, enter 9999):

60

A.2.2. Total number of subjects to be studied by the UNC-CH investigator(s) (provide exact number; if unlimited, enter 9999):

60

A.2.3. If the above numbers include multiple groups, cohorts, or ranges or are dependent on unknown factors, or need any explanation, describe here:

Subjects for this study will be healthy 18-35 year-old male and female subjects. Our recruitment goal is for 60 subjects to complete this study protocol. Subjects will be recruited through the FEFA Inc (see recruitment section).

A.2.4. Do you plan to enroll subjects from these vulnerable or select populations:
If you will include children, prisoners or nonviable neonates or neonates of uncertain viability, please check the appropriate category below and complete the additional sections.

You should check "Pregnant women" if you specifically intend to recruit women who are pregnant or are not excluding pregnant women in biomedical research that is greater than minimal risk. Do not check if you are conducting a survey of the general public or conducting secondary data analysis or chart review not aimed at pregnant women.

Only check UNC-CH Student athletes, athletic teams, or coaches if you have specific plans to enroll these subjects. This is not applicable for intramural or club sports. For definitions and guidance see SOP 1201: Vulnerable subjects in research.

✖ Children (under the age of majority for their location)
Any minor subject who attains the age of majority during the course of the research study must provide consent as an adult, unless consent has been waived, which is requested in section D.3.1.
✖ Pregnant women
✖ Nonviable neonates or neonates of uncertain viability
✖ Prisoners, others involuntarily detained or incarcerated (this includes parolees held in treatment centers as a condition of their parole)
If an enrolled participant becomes incarcerated during the course of the research, they must be removed from the research project until such time as the IRB (and OHRP for NIH funded projects) approves the study to include prisoners, unless there is an immediate risk to the participant from ending treatments under the protocol.
✖ UNC-CH Student athletes, athletic teams, or coaches

A.2.5. Based on your recruitment plan and target sample population, are you likely to include any of the following as subjects? Select all that apply. This is not applicable to secondary data analysis or chart review.

Based on your responses, the consent form builder will insert the required text into your consent form template.

✖ Decisionally impaired individuals
(e.g., Mini mental state examination (MMSE), Montreal cognitive assessment (MOCA))
✖ Children who are wards of the State (Foster children)
✖ Non-English-speaking individuals
✖ UNC-CH Students
✖ UNC-CH Employees
✖ People, including children, who are likely to be involved in abusive relationships, either as perpetrator or victim. This would include studies that might uncover or expose child, elder or domestic abuse/neglect. (See SOP Appendix A)

A.2.6. If any of the above populations are checked (excluding 'Decisionally impaired individuals' and 'Children who are wards of the State (Foster children)'), please describe your plans to provide additional protections for these subjects.

No Answer Provided

A.2.7. Age range of subjects:

Minimum age of subject enrolled	18
	years
Maximum age of subject enrolled	35
» If no maximum age limit, indicate 99	
	years

A.3. Inclusion/exclusion criteria

A.3.1. List required characteristics of potential subjects (i.e., inclusion and exclusion criteria). If not covered, list also characteristics that would preclude their involvement.

1. Age 18-35 years old healthy male and female (19? BMI?30).

2. Physical conditioning allowing intermittent, moderate exercise for 2 hours, and ability to complete the exposure exercise regimen chosen to induce an minute ventilation rate of 20 L/min/m^2 for 15 minutes without exceeding 80% of predicted maximal heart rate.

3. Normal resting ECG.

4. Normal lung function

i. Forced vital capacity (FVC) ? 80% of that predicted for gender, ethnicity, age and height at the time of physical examination, and prior to air and ozone exposures.

ii. Forced expiratory volume in one second (FEV_1) ?80% of that predicted for gender, ethnicity, age and height at the time of physical examination, and prior to air and ozone exposures.

iii. FEV_1/FVC ratio ?80% of predicted values at the time of physical examination, and prior to air and ozone exposures.

5. Oxygen saturation greater than 94% at the time of physical exam.

6. Individuals whose blood omega-3 index is 5% or lower at the time of screening.

A.3.2. Justify any exclusion based on race, gender or ethnicity

1. Individuals with a history of acute or chronic cardiovascular disease, chronic respiratory disease, cancer (possible exception for history of non-melanoma skin cancer), rheumatologic disease, neuromuscular disease, or immunodeficiency state.

2. Individuals with a cardiovascular disease risk score greater than 10% using the ACC/AHA ASCVD risk calculator. (Based on the 10-year risk of heart disease or stroke using the Atherosclerotic Cardiovascular Disease algorithm published in 2013 American College of Cardiology/American Heart Association Guideline on the Assessment of Cardiovascular risk.)

3. Uncontrolled hypertension (>150 systolic, >90 diastolic).

4. Individuals who are diabetic (previously diagnosed or with hemoglobin A1c level >6.4%).

5. Individuals with asthma or a history of asthma.

6. Individuals who are allergic to chemical vapors or gases.

7. Individuals who have skin allergy to tape or electrodes.

8. Individuals is pregnant, attempting to become pregnant or breastfeeding.

9. Individuals who are currently smoking (including vaping, hookah and e-cigarette) or have smoking history within 1 year of study (defined as more than 1 pk/yr in the past year) or have a greater than/equal to a 5 pack year smoking history.

10. Individuals living with a smoker who smokes inside the house.

11. Individuals who are regularly exposed to high levels of vapors, dust, gases, or fumes.

12. Individuals that do not understand or speak English.

13. Individuals that are unable to perform the exercise required for the study.

14. Individuals who are taking ?-blocker medications.

15. Individuals who are allergic to fish or omega-3 fatty acids, or are on prescription of taking omega-3 fish oil as therapy.

16. Individuals that are unwilling or unable to stop taking medications that may impact the results of ozone challenge for the duration of the study. Medications not specifically mentioned here may be reviewed by the investigators prior to an individual’s inclusion in the study.

17. Individuals who are unwilling or unable to stop taking any current dietary supplements for the duration of the study. Prebiotics and probiotics are acceptable.

18. Individuals who are unwilling or unable to adhere to study specific dietary restrictions (see details under A.4.2 dietary instruction).

19. Individuals who have unspecified illnesses, which in the judgment of the investigators might increase the risk associated with ozone inhalation will be a basis for exclusion.

20. Individuals with bleeding/clotting disorders.

21. Individuals who are not willing to participate the induced sputum procedure on the training day.

Temporary exclusion criteria:

1. Individuals who have recent (within 6 month) abdominal and/or eye surgery, or with any types of hernia, as well as any other contraindications for raised intra-abdominal pressure.

2. Individuals who have had an acute respiratory illness within 4 weeks.

3. Individuals who are currently taking systemic steroids, oral anticoagulants, over-the counter pain medications (such as aspirin, Advil, Aleve) or NSAIDs, or have taken these medications within the last 14 days.

4. Individuals who have active allergies.

Use of other medications will be evaluated on a case-by-case basis. There is the potential that an individual's current medication use will preclude them from participating in the study at the current time, but they may be reassessed and potentially rescheduled for participation at a later time.

A.3.3. Will pregnant women or women who become pregnant be excluded?

Yes

If yes, provide justification and describe the type and timing of pregnancy testing to be used:

We will exclude women that are pregnant, or actively trying to become pregnant, from this study due to the unknown nature of the effects of air pollutant exposure on the fetus.

Pregnancy tests will be administrated to any female subjects who may have child-bearing potential on the training day and on the exposure day if more than 7 days since last pregnancy test it will be repeated. Women who have had permanent sterilization (tubal ligation) or who have undergone hysterectomy do not need to undergo pregnancy testing. For all other female participants, a pregnancy test should be performed, as outlined, at baseline (training) and prior to the ozone exposure.

A.4. Study design, methods and procedures

Your response to the next question will help determine what further questions you will be asked in the following sections.

A.4.1. Will you be using any **methods or procedures commonly used in biomedical or clinical research** (this would include but not be limited to drawing blood, performing lab tests or biological monitoring, conducting physical exams, administering drugs, or conducting a clinical trial)?

Yes

A.4.2. Describe the study design. List and describe study procedures, including a sequential description of what subjects will be asked to do, when relevant.

This will be a randomized, double blinded study. Treatment groups will include forty healthy young adults who will be given dietary supplementation of fish oil or olive oil for 4 weeks. A control group will consist of 20 healthy volunteers who will receive no supplements during that regiment. Fish oil supplements will consist of three pills of commercially available 1 gram enteric-coated soft-gels (gelatin capsules) formulated to deliver >60 % eicosapentaenoic/docosahexaenoic acids (EPA/DHA). Olive oil supplements will consist of three pills of commercially available soft-gels containing 1 gram of USDA organic certified, cold pressed extra virgin olive oil. Olive oil and fish oil supplements will be provided to study volunteers in sealed bottles containing 90 soft-gels, as procured from the vendor, with the original product label removed in order to preserve blinding. The UNC Investigational Drug Service (IDS) will be responsible for dispensing the supplements. The EPA medical station nursing staff will conduct the randomization and keep the assignments blind to the study investigators.

Each subject will be blindly exposed to clean air for 2 hour on the first day, and then ozone for 2 hours on the second day in an exposure chamber after the 4 week supplementation period. The subjects will exercise to a minute ventilation of approximately 20 L/min/m^2 body surface area for every other 15 min alternating with resting period for a total of 1 hour exercise per chamber exposure.

A follow-up visit will be scheduled approximately 18 hours after the second exposure.

The subjects will be asked to comply the following requirements:

1) No over-the-counter pain medications such as aspirin, Advil, Aleve or other non-steroidal anti-inflammatory medications for 2 weeks prior to exposure.

2) Avoid smoke and fumes for 24 hours before all visits.

3) Avoid exposure to unvented household combustion sources (gas stove, lit fireplaces oil/kerosene heaters) for 48 hours before all visits.

4) Avoid exposure to ozone-based home air purifiers for 24 hours before all visits.

5) Avoid drinking alcohol 24 hours before all visits.

6) Avoid strenuous exercise for 24 hours prior to and after all visits.

7) Eat a light breakfast and low-fat lunch on the exposure days.

8) Do not eat pan fried and/or grilled foods after midnight prior to the exposure days.

9) Do not consume caffeine for 12 hours prior to all study visits.

Screening and general physical exam

Subjects will be recruited by the FEFA Inc (IRB approved protocol 95-0518, see recruitment section). During an initial telephone interview, the subjects will receive information regarding the study and their eligibility status will be assessed. Subjects whose responses indicate that they are likely to meet the criteria will be scheduled for an appointment in the medical station in the US EPA Human Studies Facility (HSF) for a physical exam (IRB approved protocol 95-0518), and a screening for omega-3 index (consent form OMG-1). During the screening, volunteers will be tested the blood level of omega-3 index by using a commercially available omega-3 index measurement kit.

Training

Subjects who are not excluded from the initial screening and physical exam will be instructed to call UNC outpatient registration to get a medical record number if they do not have one. The number is for UNC IDS dispensing supplements. Then subjects will be scheduled for training in the HSF. They will be required to wear comfortable clothes and sneakers as they will undergo exercise training. During this visit, the study protocol will be outlined and informed consent obtained to initiate the study. Subjects' exposure sessions will be scheduled. Consent forms for 1) main study consent (form OMG-2), 2) genotyping of GSTM1 (form OMG-3), 3) storing blood with identifying information (form OMG-4), 4) allowing to re-contact following removal from the Study (form OMG-5), 5) Center for Environmental Medicine, Asthma and Lung Biology Repository for Storage of Coded Samples (form OMG-6, IRB approved protocol 05-2528), and 6) consent checklist (form OMG-7) will also be signed. The subjects identified from a previous study (IRB13-1644, IRB13-0459) will not need genotyping for this study. The subjects may ask any questions they have regarding their participation in the study. Pregnancy test and a menstrual history will be collected on female subjects with child-bearing potentials. Baseline measures and training will also be conducted.

1. ***Urine cotinine test:*** Urine samples may be collected for cotinine test at the discretion of the medical staff.

2. ***Pregnancy tests*** will be administrated to any female subjects who may have child-bearing potential on the training day and on the exposure day if more than 7 days since last pregnancy test it will be repeated.

3. ***Baseline measures:*** subjects will undergo blood pressure and pulse oximetry. Approximately 60 ml blood will be collected for analysis.

4. ***GSTM1 genotyping***: GSTM1 genotyping will be done on DNA samples. Whole blood (about 5 ml) will be collected for DNA extraction, and polymerase chain reaction (PCR) will be run to determine whether the subject carries the GSTM1 gene.

5. ***Spirometry:*** This test assesses pulmonary function by measuring the volume of air that is exhaled and the rate of airflow during exhalation after a maximal inhalation. The subjects will inhale as deeply as possible, then exhale as rapidly and completely as possible into the spirometer.

6. ***Exercise training:*** Subjects will be trained on the ergometer (treadmill or stationary bicycle) and the workload to elicit a minute ventilation (inspiration) normalized for body surface of approximately 20 L/min/m^2 body surface area. In most participants, this may be 40 L/minute. In addition, blood oxygen saturation will be monitored, and should be ? 92% during the whole exercise period. At any time, if the participant feel chest pain, shortness of breath, or other signs of distress, training activity will be immediately terminated, and the on-duty physician will assess the physical state of the volunteer.

7. ***Induced sputum:*** This procedure will be conducted to collect lower airway secretion samples. Subjects will be asked to breath in hypertonic saline solutions starting from 3% from an ultrasonic nebulizer through a mouthpiece for 7 minutes. Then they will be asked to come off the mouthpiece and be asked to gargle, clear the throat, blow the nose, and then cough samples from deep in the chest and spit it into a cup. The spirometry test will be performed to check subject's lung function. Then the subject will inhale 4% saline for 7 minutes, and repeat the cough/spirometry test procedure. Finally subject will inhale 5% saline, and again perform the cough/spirometry test. If the subject's pulmonary function (FEV_1) drops greater than 10%, but less than 20% from the baseline during any spirometry tests, next saline concentration will not be proceed. If FEV1 drops equals to or greater than 20% from the baseline, this whole procedure will be stopped immediately. We will closely monitor the subject's lung function till it returns to the baseline. Food should be avoided for 2 hours prior to the test as food residue in the mouth may contaminate the samples.

8. ***Food frequency questionnaire in the study***: Subjects will take a Food Frequency Questionnaire (form OMG-8 is the paper form) electronically to assess the food intake in the past year. This information will be used for post-study analysis only. An instruction sheet (OMG-16) will be given to help subjects complete the questionnaire.

9. ***Omega-3 intake assessment***: Subjects will complete a dietary assessment (form OMG-9) focused on their dietary intake of omega-3 fatty acids.

10. ***Dietary instruction:*** Forty subjects will be randomly given either fish oil or olive oil supplements. They will be asked to take these supplements at dinner for 4 weeks. The control group (20 subjects) will not receive any dietary supplements during that 4 weeks period. In addition, all participants will be asked to eliminate use of nutritional supplements containing omega-3 fatty acids such as fish oil supplements, and avoid all types of fish and shell fish, walnuts, flaxseeds and flaxseed oil, rapeseed oil, canola oil, soybeans and soy products, omega-3 fortified foods, cod liver oil, red wine, grape juice, and olive oil for 6 weeks (listed in the Study Preparation Sheet, form OMG-12). Subjects will be asked to write three 3-day food records (one 3-day record every other week during the 6 week dietary restriction period, form OMG-10). The 3-day food records should include three consecutive days (Thursday, Friday, and Saturday) of intake. Everything consumed during this 3-day period should be recorded, including all foods, beverages and nutritional supplements. We will provide a handout for the subjects with instruction on completing the record and estimating portion sizes (form OMG-13) with photographs of various portion sizes. Subjects should be aware that they may be contacted by telephone for clarification of ambiguous information. Completed records will be collected and analyzed.

During the study, the study team will contact the volunteers to remind them complete the dietary questionnaire and the 3-day diet diary.

An instruction of exposure session (form OMG-14) and a low fat lunch menu (form OMG-11) will also be given to volunteers at the end of this training session.

Depending on where the subjects are in the study timeline, it may be possible to reschedule the subjects if they have experienced an illness and they cannot continue taking the supplements during the 4 weeks of supplementation period. If it is decided that we can reschedule the subjects, we will give them another 4-weeks supply of either fish oil, olive oil, or placebo supplements, and they will need to restart the supplements approximately 4 weeks after their health are back to normal.

We anticipate performing several clinical procedures during the course of this study that include primary,

secondary and exploratory endpoints. However, circumstances beyond our control may arise (i.e. equipment failure) which may prevent performing a specific procedure on an individual subject. It is possible that not all procedures will be performed on every subject. If we are unable to perform a procedure which is a primary endpoint, then the patient will be compensated for all procedures and time completed on that day and rescheduled. If, however, a procedure involving collecting data in support of a secondary or exploratory endpoint could not be performed and this procedure is also a source of compensation for the subject, the subject would be compensated for that procedure but not rescheduled to make up the procedure.

Exposure Day

We will also contact subjects a few days before the exposure session to remind them of their scheduled visits. Subjects will be asked to bring the left-over pill (if they are assigned to the treatment groups) with the bottle on the 2nd exposure day.

Pre-exposure: On the day of the exposure, the subject will report to the medical station in the HSF at which time the general health of the subject will be evaluated and the pre-exposure measurements (vital signs, heart rate variability (HRV), endothelial cell function by brachial artery ultrasound (BAU), retinal photo by retinal camera, pulmonary function by spirometry, and blood sampling will be completed. Pregnancy test will be administered to all female subjects.

1. ***HRV measurement*** will be done by a Holter monitor. Electrodes for HRV measurement will be placed. The skin in the areas of electrode placement will be cleaned and shaved (if necessary) to ensure that the electrodes will remain securely attached. These electrodes will be connected to a Holter monitor. At the end of the day, the Holter monitor will be removed. It is preferable that the electrodes remain for 2.5 days, however, subjects will be given the option to remove the electrodes by the end of each exposure day. Standard telemetry leads will also be placed, and removed when the patient leaves for the day. The subjects will then be allowed to relax for 20 minutes in a reclined position after which a 10-minute resting HRV measurement will be obtained. The subjects will be instructed to avoid strenuous activities while wearing the Holter monitor.

2. ***Brachial artery ultrasound*** is to evaluate flow-mediated dilatation which will be performed in the HSF at EPA using an Acuson Sequoia with 15 mHz probe ultrasound machine. The diameter of the brachial artery will be measured at baseline and during reactive hyperemia. The subject will lie supine, and blood pressure will be measured 3 times after 15 minutes of supine rest. A pneumatic tourniquet will be placed around the right lower arm proximal to the target artery. Gated baseline images of the brachial artery will be acquired. The pneumatic cuff will then be inflated to a pressure of 50 mm Hg above the systolic pressure for 5 minutes, and increased flow will be induced by sudden cuff deflation. A second scan will be performed following deflation. Images of the brachial artery will be acquired and stored on a personal computer, and subsequently analyzed using a semi-automated offline quantification system.

3. ***Retinal image*** will be taken using an FDA-approved, commercially available, non-mydriatic fundus camera, Canon CR-2. Images will be taken from both eyes, before and after each exposure and on the follow-up day. Imaging may have to be repeated (up to 3 times per eye per session) as needed for optimal image quality (i.e., to correct for poor focus, contrast, brightness) caused by the subject moving or blinking during image acquisition. No dilation of the pupils will be required. Glasses or contacts have to be removed for this procedure.

4. ***Pulmonary function*** will be measured by spirometry.

5. ***Blood sampling*** **:** Approximately 60 ml blood sample will be collected for analysis.

6. ***Symptoms questionnaire*** (form OMG-15) before the exposure will be collected electronically.

Exposure:

All exposures will be carried out at the EPA Human Studies Facility on the UNC campus. Subjects will be monitored continuously by the EPA personnel. A duty physician will be in the facility, and can be overhead paged as needed. The subjects will be able to end their exposure and exit the chamber at any time if they choose to end their participation in the study.

The subjects will be blindly exposed to the clean air (a sham of 100ppb O_3 for 5 min will be added at the

beginning of the exposure) for 2 hours on the first day, then ozone (mean concentration of 300ppb, +/- 30ppb) for 2 hours on the second day after the 4 weeks dietary supplementation. The exposure atmosphere will be at approximately 40% ± 10% relative humidity and approximately 22 ± 2 ºC. Clean air will be passed through an air purification system to ensure minimal presence of ozone, organic vapors, or particles. Ozone concentration will be monitored continuously in real time.

During the exposure, moderate exercise will be carried out on an ergometer (stationary bicycle or treadmill) in the chamber every other 15 minutes alternating with resting period for a total of 1 hour of exercise per chamber exposure. Ventilation rate measurements will be taken during each exercise session to monitor inspired ventilation rates. The target inspired ventilation rate is 20 L/min/ m^2, which in most individuals this may be 40 L/min. Subject will be monitored continuously by visual camera. Heart rate and oxygen saturation will be monitored by telemetry and pulse oximetry.

If severe weather or other unforeseen situation arises, we will reschedule the subject for the exposure. Under these circumstances, it is possible that 2 subjects will be exposed simultaneously in the same chamber. The chamber used in this study is designed to accommodate up to four volunteers at the same time.

Subjects will be asked to bring the left-over pills (if they are assigned to the treatment groups) with the bottle on the 2nd exposure day.

Immediate Post-exposure:

Symptom questionnaire after exposure will be collected electronically. Blood pressure, pulmonary function test, brachial artery ultrasound, retinal photos, induced sputum, and HRV will be measured and approximately 60 ml of blood samples will be collected.

Follow-up visit:

Approximately eighteen hours after the second exposure, the subjects will return to the HSF to undergo a brief medical evaluation, including blood pressure, spirometry (pulmonary function testing), BAU, and retinal image. The subject will then be allowed to relax for 20 minutes in a reclined position, after which a 10-minute resting HRV measurement will be obtained, and approximately 60 ml of blood will be taken. Symptom questionnaire will also be collected electronically.

Outcomes:

Pulmonary Function will be measured before and after exposure. Subjects will perform spirometry, and will be asked to inhale as deeply as possible, then exhale as rapidly and completely as possibly into the spirometer. FVC, FEV1, and FEV1/FVC ratio values must be ? 80% of predicted on training day, air exposure day, and ozone exposure day.

Heart Rate Variability (HRV) data will be gathered using a Holter monitor. Specific 10 minute epochs to be analyzed for frequency domain variables include times immediately prior to exposure, immediately following exposure, and on the follow-up visit. Both time and frequency domain variables will be analyzed.

Flow-Mediated Dilatation (brachial artery ultrasound) Changes in diameter of arteries caused by reactive hyperemia (endothelium-dependent vasodilatation) will be expressed as a percent change in diameter relative to resting baseline values.

Retinal Imaging will be taken before and after exposure. Diameters of retinal arteries and veins will be measured from the retinal photos of one eye.

Induced Sputum Sample will be collected on the training day, and after each exposure. Samples will analyzed for cellular components and infective agents.

Peripheral Venous Blood S ample will collected before and immediately after (within 1 hr after exposure ends) each exposure, and on the follow-up visit. Blood will be drawn by the standard venipuncture technique. For venipuncture, the site is prepared with isopropyl alcohol. A tourniquet is applied. Blood is drawn from an antecubital or other appropriate vein. Endpoint measurements will include, but not be limited to, the

following: omega-3 fatty acid level, biomarkers for specific and non-specific immune responses, coagulation factors, and vasoactive factors.

In this study, our primary endpoints will be pulmonary function, HRV measurement, fatty acid and total cholesterol analysis. Our secondary endpoints will be endothelial cell function, diameters of retinal arteries and veins, and airway inflammation.

A.4.3. If subjects are assigned or randomized to study "arms" or groups, describe how they are assigned.

- *Describe the methods of computing the randomization schedule (if any) and maintaining blinding (if any).*
- *Who will perform these computations?*
- *How will you verify each subject's eligibility prior to randomization?*

This will be a randomized, double-blinded study. Sixty study subjects will randomly receive fish oil (20 subjects) or olive oil (20 subjects) supplements, or no supplements (20 subjects) for 4 weeks. The olive oil and fish oil supplements will be provided to study volunteers in sealed bottles containing 90 soft-gels, as procured from the vendor, with the original product label removed in order to preserve blinding. The UNC IDS will be responsible for dispensing the supplements, and the EPA medical station nursing staff will conduct the randomization and keep the assignments blind to the study investigators.

A.4.4. Describe any follow up procedures.

Approximately eighteen hours after the second exposure, the subjects will return to the HSF to undergo a brief medical evaluation, including blood pressure, spirometry (pulmonary function testing), BAU, and retinal image. The subject will then be allowed to relax for 20 minutes in a reclined position, after which a 10-minute resting HRV measurement will be obtained, and approximately 60 ml blood will be taken. Symptom questionnaire will also be collected electronically.

A.4.5. Once this study has been approved by the IRB, for how many months or years will this study be active (you are collecting data or have access to identifiers)?

It is anticipated that the duration of this study will be approximately 2 years. Subject recruitment and screening is expected to be continuous throughout the study until the intended number of subjects is reached. Scheduling constraints imposed by concurrent studies in the U.S. EPA Environmental Public Health Division are expected to limit the rate at which subjects can be enrolled to approximately 1-2 subjects per week.

A.4.6. Will this study use any of the following methods?

✗	Audio Recording
✗	Video Recording
✗	Behavioral observation - (e.g., Participant, naturalistic, experimental, and other observational methods typically used in social science research)
✗	Pencil and paper questionnaires or surveys
✓	Electronic questionnaires or surveys
✗	Telephone questionnaires or surveys
✓	Interview questionnaires or surveys
✗	Other questionnaires or surveys
✗	Focus groups
✓	Diaries or journals
✗	Photovoice
✗	Still photography

A.4.7. If there are procedures or methods that require specialized training, describe who (role/qualifications) will be involved and how they will be trained.

Spirometry will be performed by a qualified professional with experience in both clinical and research duties.

Venipuncture will be performed by a qualified professional registered nurse (RN) or a qualified professional.

Placement of the ECG electrodes will be done by a qualified professional with experience in both clinical and research duties.

Heart rate variability will be collected by a qualified professional with experience in both clinical and research duties.

Brachial artery ultrasound will be performed by a qualified professional with experience in both clinical and research duties.

Retinal Imaging will be performed by a qualified professional with experience in both clinical and research duties.

Dietary instruction will be given by a qualified professional with experience in both clinical and research duties.

Controlled air pollutant exposure conditions will be monitored by an engineer with several years of previous experience in contolled human exposure studies at the EPA Human Studies Facility.

A.4.8. Are there cultural issues, concerns or implications for the methods to be used with this study population?

No

A.4.A. Biomedical methods and procedures

A.4.A.1. Is this an interventional study?

Yes

Distinguish what is being done specifically for this research from procedures that would be done anyway for clinical care:

All procedures listed in this protocol are specifically for research purpose, however, they can be also found in clinical settings. We will perform routine clinical procedures including measuring blood pressure and collecting venous blood, as well as specialized clinical procedures, such as measuring heart rate variability, assessing brachial artery diameter and retinal venule and arteriole diameter, and using spirometry to evaluate lung function.

A.4.A.2. Is this a Clinical Study?
Check YES if this study involves research using human volunteers that is intended to add to medical knowledge. There are two main types of clinical studies: clinical trials and observational studies. Do NOT check yes merely because you are conducting research in a clinical setting or using clinical data.
Click here for additional definition of "Clinical Study"

Yes

Will this clinical trial be listed in ClinicalTrials.gov, either by you or the sponsor?

Yes

Choose the appropriate Phase designation for this clinical trial.

- ✖ Pilot Study
- ✖ Phase I
- ✖ Phase I/II
- ✖ Phase II
- ✖ Phase III

✗ Phase IV

✓ Other

If other, please explain

Clinical research involving human exposure to environmental pollutants

A.4.A.3. If the study involves the use of placebo control, provide justification

The control group will consist of 20 healthy volunteers who will not receive any dietary supplements.

A.4.A.4. Will this study involve drugs, biologics or other substances (such as a botanical or dietary supplement)? For guidance on dietary supplements, see Section VI, C FDA guidance document UCM229175.pdf

Yes

Please list all drugs/biologics or other substances to be administered. Provide separate entries for combination drugs and describe in procedures. For complicated dosing schedules (e.g., dose escalation studies), provide range below and detailed information in procedures.

Generic Name	Brand Name	Dose (a)	Frequency (a)	Route(s)	Status of Drug	Detail
Fish oil		3 g/d	daily	oral		view
Olive oil		3 g/d	daily	oral		view

A.4.A.5. Is there an Investigational New Drug application (IND) for this study?

Yes or Pending (Investigator Initiated)

Upload all FDA correspondence as it relates to the initial IND submission (e.g., If the FDA requested changes or clarification, please also include this correspondence along with your response to the FDA).

IND # for this specific study, if available (Note: Not the IND# associated with the DRUG):

71475

Name of the party holding the IND (as listed on FDA Form 1571)

David Peden

A.4.A.6. When the intent of a clinical investigation is to collect information about the safety or effectiveness of a device, the need for an Investigational Device Exemption (IDE) must be evaluated. Please review the Investigational Device Guidance document prior to completing this section. Your response to the following questions will determine if an IDE is needed.

A. Select the response that best describes your investigation:

5. None of the above.

A.4.A.7. Does your study involve any of the following? (check all that apply)

✗ Embryonic stem cells

✗ Fetal tissue

✓ Genetic testing (see GINA and GWAS)

✗ Clinical laboratory tests

If McLendon Labs will do the testing, you must complete the appropriate form found at UNC Health Care and submit to them for review.

✗ Testing for communicable diseases that have mandated reporting requirements (link to state guidance)

✗ Point of Care Testing (POCT), which is CLIA-approved testing done at the "bedside" or site of care by hospital or clinic personnel (not by subject). Examples include urine pregnancy testing, glucose monitoring, etc.

If McLendon Labs will do the testing, you must complete the POCT form found at UNC Health Care and submit to them for review.

✖ If your study utilizes **radiopharmaceuticals** to address basic science questions, an IND is not necessary.
Instead, your study will be reviewed/approved by the Radioactive Drug Research Committee (RDRC); approval by the Radiation Safety Subcommittee (RSS) is not required.
If you have questions about the RDRC approval process, please contact Dede Corvinus.

✖ Diagnostic or therapeutic ionizing radiation, or radioactive isotopes (not covered under 21 CFR 361.1), which subjects would not receive otherwise if not participating in this research study. Do not check if all radiation is administered as standard of care. Do check if your study includes views/scans that represent no greater than minimal risk as determined by the Radiation Safety Sub-committee. Application for Human Use of Radiation in Research.

✖ Gadolinium administered as a contrast agent

✖ Recombinant DNA or gene transfer to human subjects

✖ Any research activities conducted in the UNCHC Perioperative areas. This includes Pre-care, Pre-op, Operating room and PACU.
You must complete the Checklist for Perioperative Services and return it to moe_lim@med.unc.edu

✖ Any form of medical imaging (ultrasound, MRI, CT, X-ray, PET-CT, PET-MRI)

A.4.A.8. Will your study involve storage of specimens for future unspecified research?

Yes

Please explain:

Separate storage consent form will be included.

Will any personal identifiers or codes be retained with the specimens that would allow anyone to link the specimen back to an individual subject?

Yes

A.5. Benefits to subjects and/or society

A.5.1. Describe how this study will contribute to generalizable knowledge that will benefit society.

For society, this study will provide new information on the effects of ozone on regional lung function, inflammation, and the cardiovascular system. Data from this study will help the US EPA better understand the components of air pollution that are responsible for increasing morbidity and mortality of cardiopulmonary fatality so that federal regulations can be properly set. Findings from this study will also become the potential to contribute to devising effective strategies aimed at protecting millions from the untoward effects of these pollutants.

A.5.2. Does this study have the potential for direct benefit to individual subjects in this study?

No

Consider the nature, magnitude, and likelihood of any direct benefit to subjects. If there is no direct benefit to the individual subject, say so here and in the consent form, if there is a consent form. Do not cite monetary payment or other compensation as a benefit.

Explain

Subjects will receive no direct benefit from participating in this study other than receiving a medical examination, including blood work, brachial artery ultrasound, spirometry, and an ECG. Subjects will have full access to these records. They will also gain knowledge about their responsiveness to ozone exposure and the supplement of fish oil or olive oil might protect them from air pollutant.

A.5.3. Are there plans to communicate the results of the research OR results of any clinical tests administered for the research back to the subjects?

No

A.6. Risks and measures to minimize risks

For each of the following categories of risk you will be asked to describe any items checked and what will be done to minimize the risks.

A.6.1. Psychological

- ✗ Emotional distress
- ✓ Embarrassment
- ✗ Consequences of breach of confidentiality (Check and describe only once on this page)
- ✗ Other

A.6.2. Describe any potential psychological risks checked above and what will be done to minimize these risks

There is a possibility that participants may feel embarrassed about what they wrote on their 3-day dietary journal. The subjects will be told that these are research tools only. Results will not be revealed to anyone outside the researchers on the protocol.

A.6.3. Social

- ✗ Loss of reputation or standing within the community
- ✗ Harms to a larger group or community beyond the subjects of the study (e.g., stigmatization)
- ✓ Consequences of breach of confidentiality (Check and describe only once on this page)
- ✗ Other

A.6.4. Describe any potential social risks checked above and what will be done to minimize these risks

Risk of breach of confidentiality is minimal. All subjects will be assigned a study number which will be used for data recording – not the subject's name. The study number is all that will be entered into computer databases. All paper files that may contain the subject's name or screening number are secure in the EPA building that has limited access 24 hours/day. Any abnormal medical findings (CBC, ECG, brachial artery ultrasound image, retinal image, spirometry) will be discussed with the volunteer and the volunteer will be counseled to seek treatment from his/her personal physician if indicated. Samples will be stored at the U.S. EPA HSF. A numeric coding system will be used to ensure that subjects can not be directly identified from the samples alone.

A.6.5. Economic

- ✗ Loss of income
- ✗ Loss of employment or insurability
- ✗ Loss of professional standing or reputation
- ✗ Loss of standing within the community
- ✗ Consequences of breach of confidentiality (Check and describe only once on this page)
- ✗ Other

A.6.6. Describe any potential economic risks checked above and what will be done to minimize these risks.

No Answer Provided

A.6.7. Legal

- ✗ Disclosure of illegal activity
- ✗ Disclosure of negligence

✗ Consequences of breach of confidentiality (Check and describe only once on this page)

✗ Other

A.6.8. Describe any potential legal risks checked above and what will be done to minimize these risks

No Answer Provided

A.6.9. Physical

✗ Medication side effects

✗ Pain

✓ Discomfort

✓ Injury

✗ To a nursing child or a fetus (either through mother or father)

A.6.10. Describe any potential physical risks checked above, including the category of likelihood and severity, and what will be done to minimize these risks. Where possible, describe the likelihood of the risks occurring, using the following terms:

- Very Common (approximate incidence > 50%)
- Common (approximate incidence > 25 - 50%)
- Likely (approximate incidence of > 10 - 25%)
- Infrequent (approximate incidence of > 1 - 10%)
- Rare (approximate incidence < 1%)

Describe severity of risks using the following grading scale:

- Mild- No disruption to the subject's ability to perform daily activities; may include non-prescription intervention only
- Moderate- Temporary interference with daily activities; may include prescription intervention
- Severe- Interference with daily activities; medically significant but not life threatening
- Life threatening

Examples:

Rare (< 1%) and Severe: blindness
Rare (< 1%) and Mild: dry skin, dry mouth, transient headache

If you are using these terms differently than described above, please provide your study-specific definitions.

Phase 1 trials: Due to limited experience, incidence may be better described as the number of events that have occurred in the total number of animals/humans studied.

General measures to minimize the risks: Medical screening of the potential subjects is designed to exclude those that may be at risk from the study procedures. A physician is in the facility and can be overhead paged whenever a subject is in the building. The physician will evaluate the subject as needed. HSF has a fully stocked medical station and the University of North Carolina Hospital is within a short distance from the HSF. On subsequent days after exposure subjects will be urged to contact the medical station or the physician should they experience any of the following symptoms: epistaxis, persistent cough, chest pain, dyspnea, wheezing, hoarseness, or sore throat. Risks associated with specific study procedures are as follows:

Pulmonary function tests (spirometry) are standard non-invasive techniques that are commonly used in studies of pulmonary function on populations of all ages and entail little or no risk to the subject. Subjects may cough or become dizzy during the tests, but this occurs infrequently.

ECG and heart rate variability are standard non-invasive techniques commonly used for heart rate and rhythm analysis and entail rare or no risk to the subject. Commonly, preparation of the skin for electrode placement and removal can cause temporary minor skin redness or irritation. Itching, burning, or soreness occurs infrequently in some subjects. If these symptoms persist or worsen, they will be told to contact the medical station immediately.

Retinal image is considered non-invasive. The most common side-effect being momentary visual impairment caused by the firing of the flash used by the camera resolves wthin seconds to minutes.

Sputum induction is a non-invasive measurement of airway inflammation. Subjects with difficulty breathing due to an underlying condition such as asthma or chronic obstructive pulmonary disease or upper respiratory

infection will not be included in this study. Rarely, multiple testing attempts may cause wheezing in susceptible individuals. A physician is immediately available and rescue albuterol is on hand. The whole procedure will be monitored with pulmonary function testing to ensure a return to baseline prior to subject's discharge. Coughing and on rare occasion, fever or infection has been associated with induced sputum collection.

Brachial artery ultrasound: There are no known risks associated with imaging of the brachial artery. Very commonly, occlusion of blood flow to the forearm result in mild discomfort and temporary sensations such as tingling and numbness until the blood pressure cuff is released. Approximately 0.5 % of participants develop painless petechiae in the arm which is examined and these resolve within a few days.

Venipuncture will be done by insertion of the needle. It is likely that drawing blood will cause bruising or minor pain, which usually resolves quickly. It is infrequent that the subject may feel lightheaded or even faint due to anxiety about the blood draw. Rarely, a skin infection may occur. To minimize these risks, blood is drawn by a registered nurse at the medical station. Subjects are in a reclined position and closely monitored for any signs of faintness, given liquids and food to eat if requested. If a subject experience near syncope, the duty physician will be notified, and the subject is allowed to leave the facility once he or she is stable.

Exercise: Moderate exercise (used to increase minute ventilation) presents a potential, but minimal risk of side effects including muscle soreness, cramps, or general fatigue to the subject. The chances are infrequent to very common depending on the subject's fitness level. These effects are temporary and not typically harmful to subjects. It is also possible that exercise might uncover a previously unidentified pre-existing cardiac condition that could present a health risk to a subject.

Fish oil/olive oil supplementation: Dietary supplements with fish oil or olive oil are relatively safe as a whole. We have excluded subjects who have fish allergy. Allergic reactions to olive oil have been reported, but are rare. High-dose fish oil may increase in LDL, bleeding times, and worsening of glycemic control in diabetics (who will be excluded from the study). Therefore, 3g/day in this study should not impose a significant risk to subjects who are eligible to participate. Fish oil is likely to cause gastrointestinal upset in some people. We will use enteric-coated fish oil soft-gels to mitigate this side effect of fish oil supplementation.

Ozone exposure: During and after the exposure to ozone, it is common to experience irritation of the eyes, ears, nose, throat or lungs, heartbeat changes, coughing, wheezing, shortness of breath, or increase the chance of catching a cold. These effects typically last no more than a few hours but may last longer for particularly sensitive people. Commonly, ozone exposure also induces an inflammatory reaction that may last for 24 hours after the exposure. We are not aware of any permanent or long term effects from a short exposure like this. In addition, there may be uncommon or previously unknown risks that might occur. While we cannot exclude the possibility that study participants may have an adverse reaction to breathing ozone, the concentration of ozone used in this study is 300 ppb for two hours. Other human exposure studies have utilized this concentration of ozone (300 ppb) and higher ones for many years. Additionally, the total amount of ozone that study participants being exposed to during the two-hour period is similar to what they would be exposed to in a city where the ozone level is at the current eight-hour national standard for a period of 8 hours. The current National Ambient Air Quality Standard for ozone is 70 ppb for an hour, which results in a cumulative exposure to 560 ppb ozone during the 8 hours period in the city. This is similar to a two-hour exposure to 300 ppb (cumulative exposure = 600ppb), as will be done in this study. During the exposures, subjects will be continuously monitored during the entire exposure by direct observation and video camera. An on-duty physician in the facility will be available when exposures are occurring. Heart rate, continuous electrocardiogram via telemetry, and S_pO_2 by pulse oximetry will also be monitored continuously. Indications for terminating the exposure include significant respiratory distress or dyspnea, chest or angina-like pain, significant cardiac arrhythmias, pallor, or ataxia. Subjects will be aware that they can terminate their exposure for any reason and still receive compensation for the entire session. The investigators or duty physician will end the exposure if the subject is found to be experiencing any adverse effect. Full resuscitation equipment will be available at all times during exposures and in the event of an emergency, after initial medical assessment, patients will be transported to UNC Hospitals Emergency Department for continued treatment. Air pollution in the outdoor environment is associated with adverse health outcomes, which is the motivation for doing this study. In susceptible populations like older adults (>65 years of age) or people with cardiac disease, asthma or diabetes, air pollution is associated with elevated rates of mortality and increased risk of respiratory and cardiovascular disease. However, this risk in healthy young adults is considered to be very small.

A.6.11. Unless already addressed above, describe procedures for referring subjects who are found, during the course of this study, to be in need of medical follow-up or psychological counseling

Study volunteers will be given any new information gained during the course of the study that might affect their willingness to continue participation in the study, and regarding our decision to not allow volunteers to participate in the study (e.g. physical findings, abnormal blood values, heart rhythm irregularities).

It is important to note that all forms of medical research, diagnosis, and treatment involve some risk of injury or illness. Despite our high level of precaution, the volunteer may develop an injury or illness due to participating in this study. If the volunteer develops an injury or illness determined by the on duty physician to be due to participation in this research, the EPA will reimburse the volunteer for the medical expenses to treat the injury or illness up to $5000. If the volunteer believes the injury or illness was due to a lack of reasonable care or other negligent action, the volunteer has the right to pursue legal remedy. The Federal Tort Claims Act, 28 U.S.C. 2671et. seq., provides for money damages against the United Sates when personal injury or property loss results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. By signing the consent form the volunteer does not waive any legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence.

A.6.12. Are there plans to withdraw or follow subjects (or partners of subjects) who become pregnant while enrolled in this study?

No

A.7. Data and safety monitoring

A.7.1. When appropriate, describe the plan for monitoring the data to ensure the safety of participants. These plans could range from the investigator monitoring subject data for any safety concerns to a sponsor-based data and safety monitoring board or committee (DSMB, DSMC, DMC), depending on the study. For studies that do not raise obvious safety concerns, you may still describe your plans for monitoring the study as it progresses.

The safety of participants will be monitored throughout the course of the study by the investigators and EPA medical staff. There will be monitoring of participants by either direct observation or by closed circuit television during each exposure. During each exposure, every study participant will have their heart rate and rhythm monitored by telemetry. Additionally, the participant's pulse oximetry will be monitored during the two hour exposure/exercise period. Registered Nurses will monitor the participant from the Medical Station during the exposure. Additionally, a study physician will be immediately available by pager during all study visits. A fully equipped medical-cart will be accessible at all times with resuscitation medications and equipment. In the event of an emergency during which it becomes necessary to call 911, the UNC Chapel Hill Hospital Emergency Department is in close proximity to our facility. Participants will be medically assessed before, during and at the completion of each exposure. Participants will be asked to refrain from strenuous physical activity for 24 hours before and after each exposure.

Hematologic markers (e.g. hemoglobin, electrolytes) will be measured following each visit and analyzed for abnormalities. Additionally, Holter monitor data will be downloaded within 24 hours following the study visit and will be assessed by a Registered Nurse prior to the beginning of the next exposure series. If the assessment indicates that any significant arrhythmias occurred the Holter monitoring results will be reviewed by a licensed physician. Individuals will be removed from the study if they experience arrhythmias that pose a safety risk, such as symptomatic bradycardia, sustained superventricular tachycardia, and either sustained (?30 sec or symptomatic for any duration) or unsustained (?3 consecutive ventricular beats) ventricular tachycardia. Any detected abnormality will be brought to the attention of the investigators and the medical staff who will review the information and determine if there is adequate concern to remove the participant from the study. Any abnormality detected will be conveyed to the subject with appropriate advice for follow-up with their primary care physician or sub-specialty physician, when warranted. Any Unanticipated Problem(s) (UP) or Adverse Event(s) (AE), as defined by the UNC IRB, will be reported to the IRB as directed by the published Standard Operating Procedures (19.0).
Subjects will be aware of their right to terminate their participation in the study at any time without prejudice or loss of monetary compensation.

A.7.2. If not already addressed above, describe the plans for aggregate review of unanticipated problems (including but not limited to adverse events) across all sites, in order to monitor subject safety.

After every 5 subjects have been completed there will be an interim analysis of trends of unanticipated events, adverse events (if any) and any irregularities related to the study.

A.7.3. What are the criteria that will be used to withdraw an INDIVIDUAL SUBJECT from this study or halt the research intervention (e.g., abnormal lab tests, allergic reactions, failure or inability to comply with study procedures, etc.)?

Individual participants will be withdrawn from the study if they exhibit abnormal lab test values that, in the opinion of the investigators and study physician(s), put them at a reasonable risk for an adverse reaction to any aspect of the study procedure. Individual participants will also be withdrawn from the study if they exhibit signs of physical distress (ex. chest pain or shortness of breath) during the study. Additionally, if an individual study participant exhibits an adverse reaction to O3 exposure, or is unable to comply with the study procedures, he or she will be removed from the study.

A.7.4. Are there criteria that will be used to stop the ENTIRE STUDY prematurely (e.g., safety, efficacy, unexpected adverse events, inability to recruit sufficient number of subjects, etc.)?

Yes

Please explain

The entire study will be stopped if we are unable to recruit a sufficient number of study participants. Additionally, after every five participants complete each exposure series we will assess the incidence of significant arrhythmia, such as symptomatic bradycardia, sustained superventricular tachycardia, and either sustained (?30 sec or symptomatic for any duration) or unsustained (?3 consecutive ventricular beats) ventricular tachycardia and the potential risk that they would pose to the study population. If greater than 30% cumulative for all participants that had completed that specific exposure series at the time of assessment) of study participants exhibit significant arrhythmia or lung function decrements (FEV1) greater than 40% (comparison of absolute values between pre- and post-exposure measurements) then the study will be suspended.

A.7.5. Will this study involve a data and safety monitoring board or committee?

No

A.8. Data analysis

A.8.1. Summarize the statistical analysis strategy for each specific aim.

To test the hypothesis that ozone causes adverse cardiovascular effects and omega-3 fatty acid or olive oil supplement pretreatment would alter the adverse cardiopulmonary effects. We will measure a number of endpoints (e.g., neutrophils, inflammation markers, and lung function). Several markers of the cardiopulmonary response to ozone will also be measured (e.g., blood pressure, HRV, brachial arterial diameter, change in blood vasoactivators, lung function, and coagulation factors). In this study, our primary endpoints will be pulmonary function, HRV measurement, and fatty acid and total cholesterol analysis. Our secondary endpoints will be endothelial cell function, diameters of retinal arteries and veins, and airway inflammation.

The estimated sample size is based on the assumed increase in nLF after exposure to ambient particulate matter of 12%, and an assumed complete attenuation of the observed increase with fish oil treatment for the outcome, nLF measure of heart rate variability. The false positive rate (Type I error) is 0.05.

H0: Response from the supplementation of fish oil or olive oil is equal to the response in those supplemented with placebo.

Statistical data analyses will consist of ANOVA for continuous variables and rank sum tests for non-continuous variables pre- and post-exposure. A p value of 0.05 or less will be considered significant.

Five time points are used to address the primary hypothesis and they are referred to as “pre” exposure measured on day 1 and day 2 of the study arm, “post” exposure measured on day 1 and day 2 after exposure, and “follow up” (FU) measured on day 3 of the study arm. Based on previous studies conducted by investigators at Human Studies Facility, we have accepted a convention of normalizing ”post” and ”follow up” measurements by the corresponding “pre-air” exposure measurement prior to analysis by dividing “post”/”pre” and “FU”/”pre”. The normalization helps to control for day to day variability of the baseline level in the individuals and allows us to express all endpoints as “percent of the baseline”. Responses at “post” time points between groups are compared. Similarly follow up time point measurements are compared only to follow up. Post and follow up time points cannot be compared due to diurnal variation. This study will examine secondary endpoints in a similar manner.

Missing data
We only use data for subjects that have complete data needed to test the hypothesis and do not impute missing values. From the past experiences of similar studies subjects miss an exposure arm for one out of three reasons; 1) Subjects do not return for all study arms for personal reasons, 2) Subjects may be disqualified for medical reasons, 3) Subjects may be temporarily put on medical hold for reasons such as cold, flu, or allergies. All subjects undergo physical examination and screening which contributes to only small portion of subjects missing for the first two reasons. In case of medical hold subjects are rescheduled for a later date according to the protocol. Occasionally only a portion of endpoints are not available for unpredictable reasons such as equipment failure, failed ELISA etc. In this case, only a particular set of end-points are excluded from the analysis.

Other Considerations:
To minimize the effect of unmeasured confounders a number of restrictions are imposed on study design;

- All subjects are selected or excluded according to the basis of inclusion-exclusion criteria
- All exposures are done at approximately the same time of the day following exact protocol
- All measurements are collected at approximately the same time
- All endpoints are normalized for statistical analyses.

Multiple testing, and as a consequence the potential for false-positive results, can be a problem; however, we will look at response patterns rather than statistical significance and health outcomes/markers of similar pathways (e.g. inflammatory pathway) as well as within each marker to get a consistent picture of the influence of air pollution on our health outcomes.

A.8.2. If this is a pilot study, please describe the future study and say how its study design, aims, sample size, and methods differ from the pilot study you are proposing.

this is not a pilot study

A.8.3. Provide a compelling justification for the proposed sample size in terms of the likelihood of achieving each aim.

The study is powered on the primary endpoint FEV1. To estimate the required sample size for the power of 80% with a type I error rate of 5% for a two-sided alternative hypothesis we used data from previous studies conducted by the co-investigators that detected changes in FEV1 following ozone exposure. The sample size was calculated to detect a difference of 11% change in FEV1 assuming a standard deviation of 10.2 %. Using GraphPad software, an N of 19 per group was derived using a power of 0.8 and an a of 0.05. This study will enroll approximately 60 subjects in order to provide sufficient power for the examination of differences among the three groups: fish oil, olive oil, or placebo.

A.8.4. Summarize the plans for data management.

The study investigators will be responsible for ensuring data management quality. The study investigators will assisted by their data management staff in monitoring adherence to protocol. The majority of data inputs are automated from instrumentation into databases, reducing chances of human error in data input.

Federal records will be kept in accordance with document guidelines in NHEERL-H/QA-RK95/00 and ORD's Policy for Paper Laboratory Records. Most Federal records will fall under EPA records schedule 503 "Scientific Research Project Files Related to Basic, Exploratory Research". Non-Federal records (schedule 008), such as technical reference materials and working papers and drafts, will be segregate from Federal records. Federal records will be retained according to the appropriate records schedule.

A.9. Identifiers

A.9.1. Check which of the following identifiers you already have or will be receiving, or select "None of the above."

- ✔ Names (this would include names/signatures on consent forms)
- ✔ Telephone numbers

✔ Any elements of dates (other than year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death. For ages over 89: all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 and older

✔ Any geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes (e.g. GPS coordinates), except for the initial three digits of a zip code

✘ Fax numbers

✔ Electronic mail addresses

✔ Social Security numbers

✘ Medical record numbers

✘ Health plan beneficiary numbers

✘ Account numbers

✘ Certificate/license numbers

✘ Vehicle identifiers and serial numbers (VIN), including license plate numbers

✘ Device identifiers and serial numbers (e.g., implanted medical device)

✘ Web universal resource locators (URLs)

✘ Internet protocol (IP) address numbers

✘ Biometric identifiers, including finger and voice prints

✘ Full face photographic images and any comparable images

✘ Any other unique identifying number, code, or characteristic, other than dummy identifiers that are not derived from actual identifiers and for which the re-identification key is maintained by the health care provider and not disclosed to the researcher

✘ None of the above

A.9.2. For any identifiers checked, how will these identifiers be stored in relationship to the research data?

✘ with the research data (i.e., in the same data set and/or physical location)

✔ separate from the research data (i.e., coded with a linkage file stored in a different physical location)

Provide details about the option you selected above:
All individuals who have been granted data access to perform their research-related duties have received full ethics training and will be bound by an agreement of confidentiality. All information provided by the participant to the investigators and all information that is collected about the participant by the investigators shall be kept confidential to the extent that is provided by law. Computer data files and questionnaires are on a secure password protected server and subjects are coded with an unrelated subject identifying study number. Data will be recorded on paper (charts, data sheets, strip chart recorders) and/or in electronic web-based diaries will only be linked using this study number. The participant's actual identity cannot be ascertained exclusively from these data. The participant's name will not be used in any publications. Access to the records of this study will be provided by the identifying study number only and given only to those individuals associated with the study who require access to the data to perform their duties. With signed consent from the participant, the samples will be stored indefinitely for future testing. Portions of the sample may be shared with researchers at other scientific institutions or sent to outside clinical laboratories for analysis, however, only coded samples will be sent. No personal identifiers will leave the Medical Station and all medical charts/records are maintained in a locked room in the medical records office of the 24 hr guarded year round US EPA Human Studies.

A.9.3. Are you collecting Social Security Numbers to be used as a unique identifier for study tracking purposes for national registry or database? (Do not check yes if collecting SSN *only* for payment purposes; this will be addressed later.)

No

A.10. Confidentiality of the data

A.10.1. Describe procedures for maintaining confidentiality of the data you will collect or will receive (e.g., coding, anonymous responses, use of pseudonyms, etc.).

All individuals who have been granted data access to perform their research-related duties have received full ethics training and will be bound by an agreement of confidentiality. All information provided by the participant to the investigators and all information that is collected about the participant by the investigators shall be kept confidential to the extent that is provided by law. Computer data files and questionnaires are on a secure password protected server and subjects are coded with an unrelated subject identifying study number. Data will be recorded on paper (charts, data sheets, strip chart recorders) and/or in electronic web-based diaries will only be linked using this study number. The participant's actual identity cannot be ascertained exclusively from these data. The participant's name will not be used in any publications. Access to the records of this study will be provided by the identifying study number only and given only to those individuals associated with the study who require access to the data to perform their duties. No personal identifiers will leave the Medical Station and all medical charts/records are maintained in a locked room in the medical records office of the 24 hr guarded year round US EPA Human Studies Facility.

The study data will be archived with identifiers by storage in a locked room in the 24hr, guarded year round, US EPA Human Studies Facility building. If offsite storage space is ever required for the data, the data will be transferred to offsite storage according to the US EPA's record keeping guideline.

A.10.2. Describe how data will be transmitted among research team (i.e., personnel listed on this application).

In general, information will be transmitted between the study investigators with paper, verbal, and encrypted electronic transmissions. The information will include pertinent medical history, physical examination, lab studies, and information relating to study endpoints (e.g. spirometry, and cardiac physiology data). Within the EPA building, there will be communication between the FEFA Recruitment Office and the study investigators with regards to participant qualification.

A.10.3. Are you collecting sensitive information such as sexual behavior, HIV status, recreational drug use, illegal behaviors, child/physical abuse, immigration status, etc?

No

A.10.4. Do you plan to obtain a federal Certificate of Confidentiality for this study? Please note that all ongoing or new research funded by NIH as of December 13, 2016 that is collecting or using identifiable information is automatically issued a Certificate of Confidentiality (CoC). You should also select "Yes" if your study is NIH funded and has been issued a CoC under this updated NIH policy.

No

A.10.5. If this study is limited to data collection by survey or interview, discuss the potential for deductive disclosure (i.e., directly identifying subjects from a combination of indirect IDs).

The potential for deductive disclosure is not likely in this study since the variables collected could not reasonably be used in aggregate to identify a single individual in this population.

A.10.6. Will any of the groupings or subgroupings used in analysis be small enough to allow individuals to be identified?

No

A.11. Data sharing and transmission

A.11.1. Check all of the following who will receive **identifiable data** (contains any of the 18 identifiers listed above) outside the immediate research team (i.e., not listed as personnel on this application)? *

- ✔ No one
- ✘ Coordinating Center
- ✘ Statisticians

- ✖ Consultants
- ✖ Other researchers
- ✖ Registries
- ✖ Sponsor and/or its designee(s)
- ✖ External labs for additional testing
- ✖ Journals
- ✖ Publicly available dataset
- ✖ Other

A.11.2. For any recipients checked above, explain the confidentiality measures to be taken

No Answer Provided

A.12. Post-study disposition of identifiable data or human biological materials

A.12.1. Describe your plans for disposition of data or human biological specimens that are identifiable in any way (directly or via indirect codes) once the study has ended. If you plan to destroy linkage codes or identifiers, describe how and when this will be done.

The study data will be archived with identifiers by storage in a locked room in the secured US EPA HSF building. If offsite storage space is ever required for the data, the data will be transferred to offsite storage according to the USEPA's record keeping guidelines. All specimens (except for the sputum samples) remaining after the completion of the study will be stored with only an alphanumeric specimen number identifier in a secured freezer in accordance with the EPA Human Studies Facility protocol, titled "Repository for storage of human specimens" (IRB approved protocol #07-1768). The sputum samples will go into the UNC Center for Environmental Medicine, Asthma and Lung Biology (CEMALB) repository (IRB approved protocol #05-2528) with identifying information. A separate consent form will be given to subjects for storing sputum specimens. Identifying information in records that could be used to link participants to specimen numbers will be protected by an "honest broker" system in which only EPA medical station personnel will be able to link specimen numbers to the associated personal identifying information. The honest broker system is described in Appendix O of the UNC-CH Human Research Protection Program's standard operating procedures.

Only the Principal Investigator, Co-investigator and laboratory technical staff identified on the protocol will have access to the repository. The Co-investigator will assume contingency responsibility for security of participant files, specimens, and future studies in the absence of the Principal Investigator. Specimens and data deriving from this study may be released to other investigators for more comprehensive studies with appropriate US EPA approval. In the event of their release to other investigators the specimens and/or data will carry only the alphanumeric code originally assigned and will be identifiable only to the Principal and Co-investigator. Specimens from subjects who opt not to allow for storage will be destroyed at the end of the study. Subjects at any time may request, in writing, that their samples no longer be stored in the repository. Any analysis in progress at the time of the request or already performed prior to the request being received by the researcher will continue to
be used as part of the research study. Once the researcher has obtained written notification, the requesting subject's specimens will be destroyed.

Part B. Direct Interaction

B.1. Methods of recruiting

B.1.1. Check all the following means/methods of subject recruitment to be used:*

- ✖ In person
- ✖ Join the Conquest
- ✖ MyChart

Use of MyChart for research recruitment purposes is currently available only to studies which meet specific criteria to participate in a pilot test. Please contact Stephanie Deen if you would like to see if your study meets the criteria for this use.

- ✗ Participant pools
- ✗ Presentation to classes or other groups
- ✓ Letters
- ✓ Flyers
- ✗ Radio, TV recruitment ads
- ✓ Newspaper recruitment ads
- ✓ Website recruitment ads
- ✓ Telephone script
- ✓ Email or listserv announcements
- ✓ Follow up to initial contact (e.g., email, script, letter)
- ✗ Other

B.1.2. Describe how subjects will be identified

Volunteers will be recruited for this study by the FEFA Corporation. The manner in which this will be done is similar to past U.S. EPA studies and specific recruitment procedures as per the previously UNC IRB-approved protocol, Recruitment and Screening of Potential Participants for EPA Studies (IRB #95-0518).

Potential volunteers will self identify in response to the advertising described in section B.1.1. Theexception will be for those identified from a pool of previous volunteers who are selected based on study eligibility criteria. Any previous volunteers that meet the study criteria will be contacted via an IRB approved email or phone script. After they are provided information about the study, they will elect whether or not to respond.

B.1.3. Select any of the following procedures solely conducted for screening, recruiting, or determining the eligibility of prospective human subjects. (Note: you should only collect the minimal information needed for these purposes.)

- ✓ Obtain information through oral or written communication with the prospective subject or legally authorized representative
  This includes online, telephone, or in-person screening questionnaires or interviews.
- ✗ Obtain already collected identifiable private information or records
  Examples include review of medical charts, data repositories, and administrative records.
- ✗ Reviewing/testing identifiable biospecimens by accessing stored biospecimens and related information
- ✗ None of the above

B.1.4. For any selections made, please describe the procedures. (Respond “N/A” if “None of the above” is selected.)

Volunteers will be recruited for this study by the FEFA Corporation. The manner in which this will be done is similar to past U.S. EPA studies and specific recruitment procedures as per the previously UNC IRB-approved protocol, Recruitment and Screening of Potential Participants for EPA Studies (IRB #95-0518).

B.1.5. For any information collected for these purposes, please describe when and how you will destroy the data if the participant declines to participate or is not eligible. (Respond “N/A” if “None of the above” is selected.)

All documentation and any information collected on potential human subject volunteers are kept indefinitely under EPA's official record collection, usage, and storage rules.

B.1.6. Describe how and where subjects will be recruited and address the likelihood that you will have access to the projected number of subjects identified in A.2.

Subjects will be recruited for this study by the FEFA Inc, which has recruited for studies at the U.S EPA HSF for years. The manner in which this will be done is similar that that of past U.S. EPA studies and specific recruitment procedures as per the previously UNC IRB-approved protocol, Recruitment and Screening of Potential Participants for U.S. EPA Studies (95-0518). Every effort will be made to recruit women and members of racial minority groups into this study. Subjects will be asked to call the recruitment office. During the telephone interview, the subjects will receive information regarding the study and their eligibility for the study will be assessed. Subjects who provide responses which indicate that they are likely to meet the criteria for this study, will be invited to participate in Phase I and Phase II of the Recruitment and Screening of Potential Participants for U.S. EPA Studies (IRB approved protocol 95-0518).

B.1.7. Describe how you will protect the privacy of potential subjects during recruitment

Emails will be sent from password protected computers with email stored on secure servers. Email subject lines will state either “Study at the US EPA” or “Your appointment at the EPA Human Studies Facility”. All phone calls and phone screening interviews will be conducted from private offices in the EPA Human Studies Facility. On site screening will also be conducted in private offices so that no personal information is shared with other research volunteers. More than one volunteer may be present in the waiting room at one time, but personal information will not be discussed in that area.

B.1.8. Describe how subjects will be contacted, if not addressed above

Potential volunteers will contact FEFA by phone, or by email from the recruitment web site (www.epastudies.org). FEFA will respond either by phone or by email.

B.1.9. Describe who (by role) will do the recruiting

FEFA, Inc. will provide recruitment services to support this study. FEFA is a Contract Research Organization under contract with the US EPA to provide support services for human research at the Human Studies Facility in Chapel Hill, NC. FEFA staff members are CITI and COI trained and certified.

B.1.10. Describe efforts to ensure equal access to participation among women and minorities

Every effort will be made to include women and minorities in this research. Advertising will be placed in a variety of locations to allow widespread access to recruitment information.

B.2. Protected Health Information (PHI)

Protected Health Information (PHI) is any identifiable information about the subject's health that relates to their participation in this research and is obtained from sources other than the subject, such as medical records, health care providers, insurance plans, etc. more

B.2.1. Are you requesting a limited waiver of HIPAA authorization?
If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a limited waiver of HIPAA authorization (see SOP 1801, 2.3). This does not apply to situations where you will never contact subjects directly (e.g., retrospective chart review), in which case you should request a full waiver under section D.

No

B.2.2. Will you need ongoing access to PHI (e.g., medical records) to conduct the study, beyond the identification of potential subjects as addressed above? In this case you will need to obtain a signed HIPAA Authorization from each subject.

No

B.3. Subject Contact, Duration and Privacy

B.3.1. Number of contacts per subject (contacts includes in-person, telephone, email, mailings, etc.)

Approximately 7-9

B.3.2. Duration of each contact. If multiple contacts, provide the range or average time for each contact.

Individual visits will vary between two and nine hours.

B.3.3. Total duration of individual subject's participation, including follow up evaluation, if applicable

7-8 weeks

B.3.4. Where are you studying subjects or obtaining their data?

Non-healthcare setting

B.3.5. Provide more information about the location(s) where research will be conducted (e.g., if UNC Medical Center is checked in #4 above and study visits will be conducted in the CTRC, enter "CTRC" here.)

Participants will be studied at the United States Environmental Protection Agency Human Studies Facility located at 104 Mason Farm Road, Chapel Hill, NC 27514.

B.3.6. Describe procedures that will ensure privacy of the subjects in this study. Examples include the setting for interviews, phone conversations, or physical examinations; communication methods or mailed materials (e.g., mailings should not indicate disease status or focus of study on the envelope)

All interviews and phone conversations will be conducted in private rooms in the U.S. EPA Human Studies Facility, a secure Federal Facility with 24 hour security guard service year round, people entering the facility must present a government issued photographic identification, and only individuals working in the building have access beyond the guard's desk without an escort. Physical exams and other procedures will occur in appropriate clinical areas of the EPA. Occasionally, other subjects may be seen in the clinical area at one time; however, sensitive information is only discussed in private (medication use, pregnancy test results). Subjects may be contacted by email to schedule/remind them about study visits or to answer specific questions. Any information sent via US mail or campus mail will simply have a return address, no other study specific information.

B.4. Incentives for participation

B.4.1. Are there incentives (monetary or non-monetary) for subjects to participate or are you reimbursing subjects for study-related costs (e.g., travel, parking, hotel accommodations or childcare)?

Yes

A. Please describe any incentives and/or reimbursements for study-related costs separately below.

Money received by participants in research studies is normally treated as ordinary income by taxing authorities and payments made to participants will be reported to the Internal Revenue Service as required by law. FEFA Corporation will collect participants' social security numbers for income reporting purposes as indicated in IRB #95-0518. The money is not intended to coerce completion or participation, but to emphasize the importance of all the visits, and to signify the importance of participants' time and commitment to the research study.

Subjects will receive monetary compensation for their time (approximately $12 per hour) and for procedures in the study. This amount reflects both the procedures or tests involved, and the time required to participate. In addition, subjects traveling from areas beyond Chapel Hill/Carrboro will be reimbursed for travel expenses commensurate with the US Government mileage rate in effect at the time. Parking will be provided or costs will be paid.

The following table details the expected compensation for completion of the entire study:

Training day (approximately 4 hours) $150

- Informed consent
- Blood draw
- Pulmonary function test
- Exercise training
- Induced sputum
- Dietary counseling
- Get supplement pills and instructions

Each exposure series

Exposure day 1 (approximately 9 hours) $500

- Blood draws (2X)
- Heart rhythm monitoring (2X)
- Brachial artery ultrasound (2X)

- Retinal image (2X)
- Pulmonary function test (2X)
- Induced sputum (optional) subjects who decide not to do induced sputum on exposure day(s) receive $100.00 less for this day; ($400 instead of $500)
- Lunch

Exposure day 2 (approximately 9 hours) $500

- Blood draws (2X)
- Heart rhythm monitoring (2X)
- Brachial artery ultrasound (2X)
- Retinal image (2X)
- Pulmonary function test (2X)
- Induced sputum (optional) subjects who decide not to do induced sputum on exposure day(s) receive $100.00 less for this day; ($400 instead of $500)
- Lunch

Follow up day (approximately 3 hours) $200

- Blood draw
- Heart rhythm monitoring
- Brachial artery ultrasound
- Retinal image
- Pulmonary function test

Study on-time bonus $75

Dietary compliance/Study completion $250

- Food frequency questionnaire/counseling
- 3-days food record (3X)
- 6-weeks dietary restriction and 4-weeks dietary supplementation
- Study completion

Total payment = $1675

Alternate Total payment - $1475 (Subjects who have decided not to perform induced sputum(s) on exposure days.

B. Specify the schedule for incentives and if/how this will be prorated if the subject withdraws (or is withdrawn) from the study prior to completing it.

A subject who is unable to complete the study for voluntary reasons or failure to comply with eligibility requirements will receive full compensation for his/her participation up to that point.

In the event a scheduled study activity must be cancelled by the investigators with less than 72 hours prior notice, the subject will be paid at the standard hourly rate for the time scheduled and canceled. Cancellations could occur due to adverse weather conditions, equipment failure, or other unforeseen events. When feasible, the subject will be rescheduled.

Subjects will receive the on-time bonus if they check-in to the medical station on time on both exposure days and the follow-up visit.

Subjects who opt not to perform the induced sputum procedure on the two exposure days will have their compensation reduced for that procedure.

C. For compensation in foreign currency, provide a US dollar equivalent.

All payments are in US currency.

D. Discuss the potential for coercion, given factors like the amount of the incentive, the age of the subjects, the purchasing power in foreign countries, the time involved and complexity of procedures, etc.

The compensation is not intended to coerce completion or participation, but to emphasize the importance of all the visits, and to signify the importance of the subject's time and commitment to the research study.

Based on hourly rates of compensation that were approved in other studies with similar protocols and/or levels of risk, the above-detailed pay schedule was felt to be commensurate with other existing studies' pay structure.

E. If the subjects are children who will receive the compensation, i.e., the child, the parents or both?

No children are involved in this study

B.4.2. Are you collecting Social Security numbers or ITIN for payment and/or tax-related purposes?

Yes

Check all that apply

- ✔ Processing payments greater than $200 per year, to support IRS reporting
- ✘ Processing payments of any amount through UNC-CH Accounts Payable

B.5. Costs to be borne by subjects

B.5.1. Will there be any costs that subjects will incur related to participation in the study? Do not include costs for standard care for which patients would be billed if they were not in this study. Also do not include the time spent participating in the study.

No

Part C. Existing Data, Records, Specimens

C.1. Data Sources

C.1.1. What existing records, data or human biological specimens will you be using? (Indicate all that apply or select 'None of the above'):

- ✘ Medical records in any format.

  ALERT: You must check both boxes: 1) Medical records in any format and 2) Electronic medical record using Epic, or you/your study team will not be granted access to Epic for research purposes.

- ✘ Electronic medical records using Epic, WebCIS or other electronic system
- ✘ Carolina Data Warehouse for Health (CDW-H) (for UNC and its affiliates only)
- ✘ Carolinas Collaborative Data Request and Review Committee (DRRC)
- ✘ Paper medical records

If you access the medical records of fewer than 50 patients under a full or limited waiver of HIPAA, submit a copy of your IRB approval letter and a completed Research Disclosure Form to Health Information Management (HIM). Do not submit this information to the IRB. For additional information about this process, you should contact HIM directly at : 919-595-5591 or 919-966-1225 or 919-595-5580.

- ✘ Data already collected from another research study

Were the investigators for the current application involved in the original collection?	--

- ✘ Patient specimens (tissues, blood, serum, surgical discards, etc.)

Has the clinical purpose for which they were collected been met before removal of any excess?	--

- ✘ Data already collected for administrative purposes

✗ Student records (You will need to satisfy FERPA requirements: see SOP 3101, section 3.1 for guidance)

✗ UNC Dental Records

✗ Data coming directly from a health plan, health care clearinghouse, or health care provider?

✗ Publicly available data

✗ Other

✓ None of the above

For EACH data source checked above, provide a description of the data, proposed use, how data were collected (including consent procedures), and where data currently reside.

--

C.1.2. Describe your plans for obtaining permission from the custodians of the data, records or specimens (e.g., pathology dept, tissue bank, original researcher):

No Answer Provided

C.1.3. Do the custodians of the data, records or specimens require a data use agreement?

No

C.2. Coding and Data Use Agreements

C.2.1. When you receive these data, records or human biological specimens will they be coded? Coded means identifying information that would enable the research team to readily ascertain the individual's identity has been replaced with a number, letter, symbol, or combination thereof (i.e., a code). If you will not be using existing materials, check "No."

No

Part D. The Consent Process

D.1. Obtaining informed consent from subjects

The standard consent process is for all subjects to sign a document containing all the elements of informed consent, as specified in the federal regulations. Some or all of the elements of consent, including signatures, may be altered or waived under certain circumstances. If you will be requesting a waiver answer "not applicable" for any of the following questions that will not pertain to this study. You will be asked to provide relevant information in the section below on waivers.

D.1.1. Will children under the age of majority in their locale (18 years in NC) be enrolled?
(Note: Any minor subject who attains the age of majority during the course of the research study must provide consent as an adult, unless consent has been waived, which is requested in section D.3.1.)

No

D.1.2. Will adult subjects be enrolled in your study?

Yes

Explain the process for obtaining consent from the subject.

The omega-3 screening consent will be obtained from the subjects at the time of screening; all other consent forms will be given to subjects on the training day.

The participants will be required to read and sign a consent form asserting that they have read and understood the following:

1. Participation is strictly voluntary
2. The purpose of the study including the societal benefits
3. The nature and extent of participation
4. Rights to withdraw from the study at any time
5. Right to privacy
6. The risks associated with participation
7. The method and schedule of compensation
8. The limits of liability with respect to the EPA and the PI.

The PI, Co-Investigator or study coordinator will then review the contents of the consent form and go through a check list highlighting important points from the consent form and answer any questions that the volunteer may have before the volunteer signs it. Subjects will have the opportunity to ask questions at any time during the study by contacting the PI, Co-Investigator, study coordinator or Medical Station. The subject will be given a copy of the signed consent form for his/her records.

D.1.3. Will decisionally-impaired subjects be enrolled in your study? (includes unconscious patients, some psychiatric disorders, others who lack the capacity to give consent)

No

D.1.4. Are you planning to obtain consent from any Non-English speaking subjects?

No

D.1.5. Describe who (by role) will be obtaining consent or parental permission.

One of the individuals listed on the front page of the application in the role of study Principal Investigator, Co-investigator, or Study Coordinator will be responsible for obtaining informed consent from the study volunteers.

D.1.6. Discuss the potential for influencing the subject's decision to participate. Describe steps that will be taken to minimize undue influence during the consent process. These might include a waiting period between the initial consent discussion and obtaining consent, or obtaining consent by someone other than a person with perceived authority (e.g., professor, employer, treating physician).

Informed consent will not be obtained during the initial phone/letter contact. This will occur at the training visit prior to enrollment into the study. Informed consent will be obtained by the Principal Investigator, a study Co-investigator, or Study Coordinator all of whom have had no prior contact with the subject.

The potential subject will be informed that they can take as much time as needed to read the consent form and that they should not sign until all their questions have been addressed.

D.1.7. Has the sponsor of this study provided a model consent form?

No

D.2. Waiver of written documentation of informed consent

The default is for subjects to sign a written document that contains all the elements of informed consent. Under limited circumstances, the requirement for a signed consent form may be waived by the IRB. For example, this might occur for phone or internet surveys, when a signed consent form is either impractical or unnecessary, or in circumstances where a signed consent form creates a risk for the subject.

D.2.1. Are you requesting a waiver of any aspect of written (signed) documentation?

No

D.3. Full or partial waiver of consent

The default is for subjects to give informed consent. A waiver might be requested for research involving only existing data or human biological specimens. More rarely, it might be requested when the research design requires withholding some study details at the outset (e.g., behavioral research involving deception). In limited circumstances, parental permission may be waived. This section should also be completed for a waiver of HIPAA authorization if research involves Protected Health Information (PHI) subject to HIPAA regulation, such as patient records.

D.3.1. Are you requesting any of the following:

✘ a waiver of informed consent in its entirety

✘ a waiver or alteration of some of the elements of informed consent

✘ a waiver of HIPAA authorization (If you are accessing patient records for this research, you must also request a waiver of HIPAA authorization)

D.3.2. If your request for a waiver applies to some but not all of your subject groups and/or consent forms, please describe and justify

No Answer Provided

D.3.3. Does this request for waiver support a study design that involves deception or withholding of information?

No Answer Provided

Consent Forms

This submission requires the following consent forms

Template Type
Adult Consent Form
SSN Collection for payments **I am not using this template because:** Not Yet Available / Not Applicable
Stored Specimens with Identifiers

This submission includes the following consent forms

File Name	Document Type
OMEGOZ-consent_Modified_03-05-18_OMG2.docx	Adult Consent Form
OMEGOZ-ConsentChecklist_Modified_03-05-18_OMG7.docx	Other Consent Materials
OMEGOZ-Genotyping_Modified_03-05-18_OMG3.doc	Other Consent Materials
OMEGOZ-Omega-3_Screening_03-05-18_OMG1.doc	Other Consent Materials
OMEGOZ-Re-contactConsent_Modified_03-05-18_OMG5.docx	Other Consent Materials
IRB_05-2528_CF_11jun2013-5.docx	Stored Specimens with Identifiers
OMEGOZ-Storage_consent_Modified_03-05-18_OMG4.doc	Stored Specimens with Identifiers

view consent forms

Attachments

This submission requires the following attachments

Document Type
Other Study Protocol **This attachment not provided because:** Not Yet Available / Not Applicable
Scientific Review Committee Approval Letter **This attachment not provided because:** Not Yet Available / Not Applicable
Electronic Questionnaire Survey
Interview Questionnaire Survey
Diaries Journal Guide
IDS Approval **This attachment not provided because:** Not Yet Available / Not Applicable
Investigator Brochure and/or Drug Package Insert **This attachment not provided because:** Not Yet Available / Not Applicable
IND Acknowledgement Letter from FDA
Letter for Recruitment **This attachment not provided because:** Not Yet Available / Not Applicable
Flyer for Recruitment **This attachment not provided because:** Not Yet Available / Not Applicable
Newspaper Ad for Recruitment **This attachment not provided because:** Not Yet Available / Not Applicable
Website for Recruitment **This attachment not provided because:** Not Yet Available / Not Applicable
Telephone Script for Recruitment **This attachment not provided because:** Not Yet Available / Not Applicable
Email or Listserv Recruitment
Recruitment Follow Up **This attachment not provided because:** Not Yet Available / Not Applicable

This submission includes the following attachments

File Name	Document Type
FishOil-OliveOil Info.pdf	Investigator Brochure and/or Drug Package Insert
FDA_Response02032017.pdf	IND Verification or Waiver from FDA
OMEGOZ Email announcement .pdf	Email or Listserv Recruitment
OMEGOZ Study Instructions FU_.pdf	Recruitment Follow Up
OMEGOZ Training Instructions FU_.pdf	Recruitment Follow Up
OMEGOZ FLYER.pdf	Flyer for Recruitment
OMEGOZ newspaper ad.pdf	Newspaper Ad for Recruitment
Automated Calls ad.pdf	Other Materials for Recruitment
OMEGOZ questionnaire.pdf	Telephone Script for Recruitment
OMEGOZ recruitment script.pdf	Telephone Script for Recruitment
OMEGOZ Web Site Oct. 2015 .pdf	Website for Recruitment
OMEGOZ Web based search ad.pdf	Website for Recruitment
Omegoz papercraigslist ad.pdf	Website for Recruitment
OMEGOZ Food Record Instructions 10-17-17.docx	Diaries Journal Guide
DHQ 10-17-17.pdf	Electronic Questionnaire Survey
Symptom questionnaire 10-17-17.docx	Electronic Questionnaire Survey
Omega-3 Assessment 10-17-17.docx	Interview Questionnaire Survey
FDA_Response02032017_1.pdf	IND Acknowledgement Letter from FDA
IDS Approval 6-20-17.pdf	IDS Approval
95-0518__Phase_I_Screening_Consent_vDec16.docx	Other
Exposure Instruction 10-17-17.doc	Other
FDA Response.pdf	Other
OMEGOZ Omega-3 index screening Appointment Email Reminder.pdf	Other
OMEGOZ Study Instructions 9_28_17.pdf	Other
OMEGOZ Study Instructions.pdf	Other
OMEGOZ payment voucher.pdf	Other
OMEGOZTrainingInstructions-Reminder 1-8-18.pdf	Other
OMG-16 DHQ Instructions for Participants 11-29-17.docx	Other
Omegoz Lunch menu 10-17-17.doc	Other
PortionSize 10-17-17.pdf	Other
SOP Isolation of genomic DNA from whole blood.docx	Other
SOP-GSTM1 Genotyping.docx	Other
SSN ExemptionMemo.PDF	Other
Study Preparation Sheet 10-17-17.docx	Other
CITI reports 6-14-17.pdf	Research Ethics Training
CITICompletionReport10-6-15.pdf	Research Ethics Training
CertificateInvestigators.pdf	Research Ethics Training
MattCitiTraining.pdf	Research Ethics Training
OutsideReview1.pdf	Scientific Review Documentation
OutsideReview2.pdf	Scientific Review Documentation

view attachments

Addenda

Data Security Requirements

view addenda

If Principal Investigator of this study is a Student or Trainee Investigator, the Faculty Advisor certifies the following:

I accept ultimate responsibility for ensuring that this study complies with all the obligations listed above for the PI.

By certifying below, the Principal Investigator affirms the following:

I will personally conduct or supervise this research study. I will ensure that this study is performed in compliance with all applicable laws, regulations and University policies regarding human subjects research. I will obtain IRB approval before making any changes or additions to the project. I will notify the IRB of any other changes in the information provided in this application. I will provide progress reports to the IRB at least annually, or as requested. I will report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. I will follow the IRB approved consent process for all subjects. I will ensure that all collaborators, students and employees assisting in this research study are informed about these obligations. All information given in this form is accurate and complete.

This study proposes research that has been determined to include Security Level 2 data security requirements. I agree to accept responsibility for managing these risks appropriately in consultation with departmental and/or campus security personnel. The Data Security Requirements addendum can be reviewed here.

Certifying Signatures:

Signature: Electronic Signature Received **Date:** 6/19/2019 01:10:51 PM

James Samet

University of North Carolina at Chapel Hill
Consent for Omega-3 Index Screening With Identifying Information

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IRB Study # 15-2960
Consent Form Version Date: March 5th, 2018

Title of Study: Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects
Principal Investigator: James Samet, PhD, MPH
Co-Principal Investigators: Haiyan Tong, MD, PhD; Wan Shen, PhD, RD, LDN; Neil Alexis, PhD.
UNC-Chapel Hill Department: US Environmental Protection Agency
UNC-Chapel Hill Phone number(s): (919) 966-0665, (919) 966-4993, (919) 843-9228
Principal Investigator Email Address: samet.james@epa.gov
Funding Source: US Environmental Protection Agency Intramural Federal Research
Study Contact telephone number(s): (919) 966-0665, (919) 966-4993, (919) 843-9228, (919) 966-6211
Study Contact email(s): samet.james@epa.gov; tong.haiyan@epa.gov; shen.wan@epa.gov, case.martin@epa.gov

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What are some general things you should know about this research study?
Research studies are designed to gain scientific information that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Research with blood, tissue and/or body fluids (specimens) can help researchers understand how the human body works. Research using specimens can also answer other questions. Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat diseases. In the future, some research may help to develop new products, such as drugs.

Details are discussed below. It is important that you understand this information so that you can make an informed choice. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
The main purpose of this research study is to determine whether fish oil or olive oil supplements can alter the cardiovascular (heart and blood vessels) and pulmonary (lungs) effects of exposure to ozone, a common air pollutant in urban environments. Results from this study will also increase our understanding of how ozone exposure adversely affects the functioning of the human cardiovascular and respiratory systems. This understanding may be especially important for patients with cardiopulmonary diseases.

The primary purpose of today's visit is to determine the level of omega-3 fatty acids in your blood, the results of which will determine your eligibility to participate in this study.

What will happen if you participate in this portion of the study?
First, you will read this consent form (Form OMG-1) and have this portion of the study described to you. You will be given the opportunity to have any questions answered before signing the consent forms. After signing the consent form, you will then be asked to wash your hands thoroughly and a small sample of your blood (between approximately an eighth to a quarter of a teaspoon) will be collected by pricking one of your fingers using a finger stick device. The blood sample will be collected by the experienced study investigator or registered nurse.

What will happen to the blood?
The blood sample will be used to measure the relative content of various fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), present in your blood.

What are the possible benefits to you?
There are no direct benefits to you for completing this portion of the study. However, you will learn about the fatty acids in your blood and have an opportunity to have any questions answered by the study personnel.

What are the possible risks or discomforts involved with being in this study?
This study might involve the following minimal risks and/or discomforts to you:

1. The risks associated with taking the blood sample is considered minimal. A registered nurse or other experienced study investigator will prick your finger using a special finger stick device designed for this purpose in order to collect the blood. The finger prick and blood collection procedure often causes momentary discomfort. Some minor bruising, which usually resolves quickly, is also possible. There is a small risk of infection. This risk is minimized by the use of sterile technique. If you develop signs of infection at the site of blood collection (redness, warmth, painful skin, or swelling), you should contact the EPA medical station immediately. In some cases, a person may faint or become sick to the stomach at the sight of blood is being collected.

2. Risk of breach of confidentiality is minimal. You will be assigned a screening number which will be used for this process – not your name. The number is all that will be entered into computer databases. All paper files which may contain your name or screening number are secure in the EPA building which has limited access 24 hours/day. A numeric coding system will be used to ensure that you cannot be directly identified from the samples alone.

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers.

Will there be any cost to you to participate?
There will be no cost to you for participating in the study. However, if you are not eligible to participate in the study for medical reasons, we may suggest that you seek follow-up care from

your own health care provider for abnormalities discovered during the screening history, physical examination, or the study. **Such care is entirely at your own expense. EPA will not provide reimbursement for any follow-up care.**

Will you receive anything for being in this study?

You will be paid $10 for participation in this portion of the study. We will give you parking coupons to cover the cost of parking. If you live outside of the Chapel Hill/Carrboro area, you will be reimbursed for mileage at the current government rate.

How will your privacy be protected?

You will be given a screening number. All electronic documents will only have that number. The paper records that the coordinators and medical staff use may have your name. Your information can be linked to your personal information by the screening number, however only study personnel have access to your personal information. Paper records which use your name are kept in a locked file cabinet in the EPA Medical Station of the Human Studies Facility. The Medical Station is locked when not attended by study staff, and the EPA Human Studies Facility has limited access to authorized individuals only, 24 hours/day for 7 days/week.

No one will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

What will happen if you are injured by this research?

All forms of medical research, diagnosis, and treatment involve some risk of injury or illness. Despite our high level of precaution, you may develop an injury or illness due to participating in this study. If you develop an injury or illness determined by the on duty physician to be due to your participation in this research, the EPA will reimburse your medical expenses to treat the injury or illness up to $5000. If you believe your injury or illness was due to a lack of reasonable care or other negligent action, you have the right to pursue legal remedy. The Federal Tort Claims Act, 28 U.S.C. 2671 et. seq., provides for money damages against the United Sates when personal injury or property loss results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence.

If a research related injury or illness occurs, you should contact the Director of the EPA NHEERL Human Research Protocol Office at 919.966.6217.

What if you are a UNC student?

You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?
Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

Who is sponsoring this study?
This research is funded by The U.S. Environmental Protection Agency. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have questions, you should contact the researchers listed on the first page of this form or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

What if you have questions about your rights as a research subject?
All research on human subjects is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously, if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_ subjects@unc.edu and/or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

IRB Study # 15-2960
Title of Study: Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects

Principal Investigator: James Samet, PhD, MPH

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate. I agree to my specimen(s) being used for omega-3 index screening with the identifying code(s).

_____ _____
Signature of Research Participant Date

_____
Printed Name of Research Participant

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent

University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Adult Subjects
Biomedical Form

OMG
2

IRB Study # 15-2960
Consent Form Version Date: March 5th, 2018

Title of Study: Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects
Principal Investigator: James Samet, PhD, MPH
Co-Principal Investigators: Haiyan Tong, MD, PhD; Wan Shen, PhD, RD, LDN; Neil Alexis, PhD.
UNC-Chapel Hill Department: US Environmental Protection Agency
UNC-Chapel Hill Phone number(s): (919) 966-0665, (919) 966-4993, (919) 843-9228
Principal Investigator Email Address: samet.james@epa.gov
Funding Source: US Environmental Protection Agency Intramural Federal Research
Study Contact telephone number(s): (919) 966-0665, (919) 966-4993, (919) 843-9228, (919) 966-6211
Study Contact email(s): samet.james@epa.gov; tong.haiyan@epa.gov; shen.wan@epa.gov; case.martin@epa.gov

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What are some general things you should know about research studies?
You are being asked to take part in a research study. To join the study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason at any time.

Research studies are designed to obtain new knowledge that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Your participation is voluntary. Deciding not to be in the study or leaving the study before it is completed will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
The main purpose of this research study is to determine whether fish oil or olive oil supplements can alter the cardiovascular (heart and blood vessels) and pulmonary (lungs) effects of exposure

to ozone, a common air pollutant in urban environments. Results from this study will also increase our understanding of how ozone exposure adversely affects the functioning of the human cardiovascular and respiratory systems. This understanding may be especially important for patients with cardiopulmonary diseases.

You are being asked to be in this study because:

- You are 18-35 years old, generally healthy.
- You have a normal resting electrocardiogram (ECG) and lung function.
- Your oxygen saturation is greater than 94% at the time of physical exam.
- Your omega-3 index is 5% or lower at the time of physical exam.

Are there any reasons you should not be in this study?

You should not participate in this study if…

- You have a history of acute or chronic cardiovascular disease.
- You have uncontrolled high blood pressure (defined as > 150 mmHg systolic or > 90 mmHg diastolic).
- You have a history of chronic lung diseases such as chronic obstructive pulmonary disease.
- You have asthma or a history of asthma.
- You have had an acute respiratory illness within the last 4 weeks.
- You have a body mass index (BMI) >30 or <19. Body mass index is calculated by dividing your weight in kilograms by the square of your height in meters.
- You are a diabetic (previously diagnosed or with hemoglobin A1c level >6.4%).
- You have neuromuscular, autoimmune, rheumatologic, or immunodeficiency disease.
- You have cancer (possible exception for history of non-melanoma skin cancer).
- You are pregnant, attempting to become pregnant or breastfeeding.
- You have allergies to fish or omega-3 fatty acids.
- You are on doctor's orders to take fish oil (we do not want to interfere with your therapy).
- You are currently taking β-blockers (such as atenolol, metoprolol, propanolol, and acebutolol).
- You are currently taking systemic steroids (such as prednisone) or have taken systemic steroids within the last 14 days.
- You have abdominal and/or eye surgery, or with any types of hernia, as well as any other contraindications for raised intra-abdominal pressure in the last 6 months.
- You are currently smoking or have a smoking history within 1 year of the study (defined as more than one pack of cigarettes in the past year) or have a greater than/equal to a 5-pack year smoking history. This includes tobacco smoking, e-cigarettes, hookah or vaping.
- You are living with a smoker who smokes inside the house.
- You are regularly exposed to high levels of vapors, dust, gases, or fumes.
- You are allergic to chemical vapors or gases.
- You have history of skin allergy to tape or electrodes.
- You have active allergies.
- You have bleeding or clotting disorders.

You should **NOT** participate if you are unable to comply with the following requirements:

- No over-the-counter pain medications such as aspirin, Advil, Aleve or other non-steroidal anti-inflammatory medications for 2 weeks prior to exposure.
- No omega-3 fatty acids or consuming more than one serving (4-6 oz) of all types of fish and shellfish, walnuts, flaxseeds and flaxseed oil, rapeseed oil, canola oil, soybeans and soy products, omega-3 fortified foods (such as omega-3 fortified eggs), and cod liver oil for the 6-week dietary restriction period.
- Avoid olive oil for cooking, dressings, and sauces for the 6-week dietary restriction period.
- Avoid drinking red wine and grape juice for the 6-week dietary restriction period.
- Stop taking any current dietary supplements for the 6-week dietary restriction period. Prebiotics and probiotics are acceptable.
- Avoid smoke and fumes for 24 hours before all visits.
- Avoid exposure to unvented household combustion sources (gas stoves, lit fireplaces oil/kerosene heaters) for 48 hours before all visit.
- Avoid exposure to ozone-based home air purifiers for 24 hours before all visit.
- Avoid drinking alcohol 24 hours before all visits.
- Avoid strenuous exercise for 24 hours prior to and after all visits.
- Eat a light breakfast and low-fat lunch on the exposure day.
- Do not eat pan fried and/or grilled foods after midnight prior to the exposure day.
- Do not consume caffeine for 12 hours prior to all study visits.
- Be willing to perform the induced sputum procedure on the training day, after undergoing induced sputum on the training day you may choose not to repeat this procedure on the exposure days. If you opt out of the induced sputum procedure on one or both of the exposure days, the reimbursement schedule will be adjusted as per the schedule at the end of this consent form.

How many people will take part in this study?

If you decide to be in this study, you will be one of approximately 60 people in this research study.

How long will your participation in this study last?

You will have up to 4 visits to the research facility over approximately 7-8 weeks if you are eligible for the study (see attached study design flow diagram).

Your participation in this study will include two parts: 1) a total of 6-weeks of dietary restriction, within which you will receive 4-weeks of dietary supplementation consisting of fish oil or olive oil, or you may be assigned to receive no pills, and 2) back-to-back exposure days in which you will undergo exposure to clean air and ozone while exercising intermittently in a specialized exposure facility, and a follow-up visit.

There is a training session (today), which will last for about 4 hours. The two exposure-day sessions which last approximately 8-9 hours each. There will also be an approximately 3-hour follow-up visit the day after your second exposure.

While your participation in this study will end after the follow-up day, you should be aware that the storage of some of your blood samples in this study may be indefinite.

What will happen if you take part in the study?

Before you agree to participate in this study, you must read this (form OMG-2) and the other consent forms (forms OMG-3 to OMG-7) in their entirety. The research and medical staff will then answer all of your questions and explain all of the risks involved in this study to your satisfaction.

You should have already undergone an initial screening visit and a general physical examination to ensure that you are a candidate for this study. You should have obtained a UNC medical record number prior to today's session. The number is used for prescribing your supplements from UNC Investigational Drug Service. If you are a female participating in this study, you will be asked about your menstrual history. Women who have had permanent sterilization (tubal ligation) or who have undergone hysterectomy do not need to undergo pregnancy testing. For all other female participants, a pregnancy test should be performed, as outlined, today and on the first exposure day.

Training Day
Today's visit is expected to last about 4 hours. We will review the inclusion and exclusion criteria and any medical conditions that you have or medications that you are currently taking. We will go over the study in detail so that you will know what we will expect from you as a participant and what you should expect from us as investigators. If you agree to participate in the study you will sign all study consent forms, and receive one set of signed copies.

You will have your vital signs checked. Approximately 60 ml (about 4 tablespoons) of blood will be collected for genotyping (with your permission), blood fatty acid and biomarker analysis. Your urine sample might be collected for cotinine analysis.

We will then train you on a breathing instrument to prepare you for your exposure session. This is known as spirometry, and you will breathe through a filter into the instrument. We will coach you, and you will be asked to take a full breath in and then blow it out as hard and fast as you can. We will ask you to do this several times. This test measures the volume of air that can be exhaled and the rate of airflow during exhalation after a maximal inhalation. Your FVC, FEV1, and FEV1/FVC values must be ≥80% of predicted.

We will also determine whether you will be able to perform the physical activity required during exposure. We will determine your ability to complete the required physical activity in two ways. First, we will determine if you are able to exercise to the protocol requirements (20 L/min/m^2 body surface area) without exceeding 80% of your predicted maximal heart rate, which will be determined relative to your age. Second, using a non-invasive method known as pulse oximetry we will determine whether you are able to exercise at the required level while maintaining a blood oxygen saturation level ≥92% (oxygen saturation is a measure of how much oxygen the blood is carrying as a percentage of the maximum that it could carry). We will monitor your

heartbeat with a safety system we have in our building called telemetry.

You will be asked to perform the induced sputum procedure, which is a method for obtaining lower airway secretions. This procedure provides a non-invasive measurement of airway inflammation. We will ask you not to eat for 2 hours prior to this test as food residue in your mouth may contaminate the samples. If you are asthmatic or have a positive methacholine challenge test, you will receive pretreatment with 2 puffs of an albuterol MDI to inhibit bronchospasm. We will ask you to breathe 3% saline from an ultrasonic nebulizer through a mouthpiece for 7 minutes while seated. You will come off the mouthpiece and be asked to gargle, clear your throat, blow your nose, and then to cough samples from deep in the chest, and spit it in a cup. We will do a pulmonary function test (PFT) to check your breathing. Then you will inhale 4% saline for 7 minutes, and repeat the cough/PFT procedure. Finally, you will inhale 5% saline, and again perform the cough and PFT's. If your PFT's drop 20% or more from your baseline, we will stop the procedure.

After these tests have been successfully performed, you will be given instructions to complete 1) an online version of dietary food frequency questionnaire (form OMG-8) to assess what food you have had in the past 12 months (an instruction sheet OMG-16 will help you to complete this questionnaire), and 2) three 3-day food records (one 3-day record every other week during the 6-week dietary restriction period, forms OMG-10 and OMG-12). You will also be asked to complete a dietary assessment (form OMG-9) focusing on your intake of omega-3 fatty acids. A list of medications, environmental exposures, and foods to be avoided in the next six weeks (form OMG-12) will be given to you. Then you will be scheduled for the exposure sessions (form OMG-14), and be given a four-week supply of fish oil or olive oil, or no pills at all.

<u>Please take 3 pills at dinner each day if you receive fish oil or olive oil pills.</u> You and your research team will not know what supplements you have received. Please do not discuss the content of the supplements with the study research team. If you receive any supplements today, please bring the left-over pills with the bottle on the 2nd exposure day.

During the study, we will contact you to remind you to complete the online dietary questionnaire and the 3-day food records. You may also be contacted by phone for clarification of ambiguous information.

Depending on where you are in the study timeline, it may be possible to reschedule you if you experience an illness and you have to stop taking the pills during this four weeks of supplementation period. If it is decided that we can reschedule you, we will give you another four weeks supply of either fish oil or olive oil and you will need to restart the pills. If severe weather or another unforeseen situation arises, we may also reschedule you for the exposures. Under these circumstances, it is possible that you will be exposed with another study volunteer simultaneously in the same chamber.

You will also tour the exposure chambers today.

Exposure days

We will call you a few days before the exposure session to remind you of your scheduled visit. You should avoid smoke, fumes, alcohol, and strenuous exercise 24 hour prior to all visits, and to abstain from pan fried or grilled meat after midnight of the exposure day.

You will be asked to eat a light breakfast and arrive at the EPA medical station by 7:30 am. Please understand that it is very important that you arrive by this time in order for the study team to process all of the samples and data. Please understand that we may have to cancel your participation if you arrive late.

Prior to exposure, you will:

- Have your vital signs checked (heart rate, respiratory rate, blood pressure, oxygen saturation level, and fill out a symptom questionnaire electronically).
- Have your heart rate variability (HRV) measured by a Holter monitor. You will have several ECG leads attached to your chest. It may be necessary to clean and shave the areas of your chest where these leads will be placed. Excessive deodorant, skin lotions, and body sprays may interfere with the function of some of these leads. Therefore, we ask you to not apply these to your chest area on the day you report to the HSF. The leads will be connected to 2 monitors (small recording devices about the size and weight of a cell phone) to obtain readings of your heart rate and rhythm. It is preferable that the electrodes will stay in place for approximately 2 ½ days as you will have this measured several times during the study, however, you will be given the option to remove the electrodes by the end of each exposure day. You will be asked to recline quietly and breathe at a constant rate for 20 minutes, after which the ECG monitor will take a 10-minute measurement of your heart rhythm. It is important that you not fall asleep during this 30-minute period. These measurements will allow us to determine whether ozone exposure causes small changes in the ability of your nervous system to regulate how your heart beats. Please avoid any strenuous activities while you are wearing this monitor.
- Have the diameter of an artery in your upper arm measured by an ultrasound machine (BAU). The ultrasound operator will scan your arm with a probe and then place a tourniquet on your arm, much like a cuff used to measure blood pressure. Measurement of the size of the artery will be made two times. First, you will be asked to rest quietly for 15 minutes, and then the first 90 second scan will be performed. Then the blood pressure cuff on your arm will be inflated for 5 minutes in order to stop the flow of blood. You may feel sensations similar to that when your foot "goes to sleep", such as "pins and needles" and tingling. After the pressure cuff is released, a second scan will be taken of the artery.
- Have your retinas imaged using an ophthalmic camera before and after each exposure, and on the follow-up visit. You will be asked to place your chin on a rest in front of the camera. We will take pictures of the inside of both of your eyes. Glasses or contacts have to be removed for this test. Please bring your own contact lens container and solutions.

- Approximately 60 ml blood drawn (about 4 tablespoons) before and after each exposure, and on the follow-up visit. We will test this blood to see if ozone affects the ability of your blood cells to function. **With your permission, we may also store some of the blood that we obtain during the study for yet-to-be-determined tests in the future.**
- Have a breathing test (spirometry). You will breathe through a filter into a clinical machine. We will coach you, and you will be asked to take a full breath in and then blow it out as hard and fast as you can. We will ask you to do this several times. This test measures the volume of air that can be exhaled and the rate of airflow during exhalation after a maximal inhalation. Your FVC, FEV1, and FEV1/FVC values must be ≥80% of predicted at the times measured in order for you to remain in the study.
- Enter the exposure chamber and be exposed to clean air or ozone.

During the exposure, you will:

Undergo exposure for 2 hours to either clean air or ozone in the chamber. The amount of ozone that you will be exposed to in the chamber is approximately equivalent to that which you would be exposed to in a city for an 8-hour period based on the current national standard. Chamber conditions will be at a comfortable temperature and relative humidity. You will do moderate exercise on an ergometer (stationary bicycle or treadmill) in the chamber every other 15 minutes alternating with resting period for a total of 1 hour of exercise per chamber exposure. A study coordinator or other trained person will be seated outside the chamber observing you at all times. During the exposure, your heart will be monitored and the amount of oxygen present in your blood will be monitored by placing a device (pulse oximeter) on your finger. If it appears you are experiencing significant discomfort, breathing or heart problems, the exposure will be terminated immediately. **In addition, you may elect to terminate the exposure at any time for any reason.** If you do so, you will be paid in full for that day's session, but will be ineligible for further participation in the study and any payments you would have received for future participation.

Immediately following the exposure, you will:

- Have your vital signs checked.
- Have a breathing test (spirometry). You will breathe through a filter into the machine. We will coach you, and you will be asked to take a full breath in and then blow it out as hard and fast as you can. We will ask you to do this several times.
- Fill out a symptom score questionnaire electronically (form OMG-15).
- Eat a low-fat lunch (form OMG-11) brought by you.
- Have blood drawn (Approximately 60 ml).
- You will recline quietly for 20 minutes, after which the ECG monitor will take a 10-minute measurement of your heart rhythm.
- Have your diameter of the artery in your upper arm reassessed.
- Retinal pictures will be retaken. Glasses or contacts have to be removed for this test. Please bring your personal contact container and solutions.

- Once you complete the above procedures, you will have about 1-2 hour waiting time before the next procedure. You can bring your personal laptop or books to use during that time. You will not be able to eat any food during this break time.
- Have samples of your airway secretions collected from the induced sputum procedure. You will be asked to breathe in different saline solutions (up to 5%) to help us get your airway samples. We will coach you, and you will gargle, clear your throat, and cough samples from deep in your chest and spit it into a cup. Your lung function will be monitored during the whole procedure. Foods must be avoided for 2 hours prior to this test.
- Be assessed and discharged by the study personnel.

Follow up visit (about 3 hours)
You will return to the HSF the next morning (approximately 18 hours after your 2nd exposure) and you will:

- Have your vital signs checked.
- Have a breathing test (spirometry). You will breathe through a filter into the machine. We will coach you, and you will be asked to take a full breath in and then blow it out as hard and fast as you can. We will ask you to do this several times.
- You will recline quietly for 20 minutes, after which the ECG monitor will take a 10-minute measurement of your heart rhythm. Electrodes will be removed from your chest at the end of this test.
- Have your blood pressure and heart rate measured.
- You will have another BAU measurement.
- Have blood drawn (approximately 60 ml) for analysis.
- Retinal pictures will be taken again. Glasses or contacts have to be removed for this test. Please bring your own contact container and solutions.
- Fill out a symptom score questionnaire electronically.

If there are any samples left over after all study information is collected, we will continue to store the samples for as yet undesignated studies. This allows us to make the best use of the samples we collect from subjects.

You will be given a separate consent form for this storage, **and you do not have to allow your samples to be stored indefinitely in order to participate in this study.**

<u>What are the possible benefits from being in this study?</u>
You will not benefit directly from being in this research study, though by participating in this study you will receive a medical examination that includes blood work, respiratory test, and ECG monitoring of heart at no charge. However, this is not a substitute for a routine doctor visit. Similarly, please note that the images of your retinas that are collected in this study will be analyzed for research purposes only and will not be reviewed or examined by an eye doctor or other medical professional. The medical staff will explain to you any remarkable findings regarding your overall health status. In addition, if we observe changes in your health status as a consequence of exposure to air pollutants, you may elect to use this information to avoid exposure on high pollution days.

This research is designed to benefit society by gaining new knowledge. Given that every member of American society is currently exposed to these pollutants, this study has the potential to contribute to devising effective strategies aimed at protecting millions from the untoward effects of these pollutants.

What are the possible risks or discomforts involved with being in this study?

This study might involve the following risks and/or discomforts to you. If you have any tendency to become uncomfortable in small closed spaces, it is possible that you may become uncomfortable during this study. You will be taken to the exposure chamber when you are first evaluated to determine your suitability for the study by allowing you an opportunity to see where you will sit and what the chamber looks like.

Ozone exposure: Breathing ozone in this study might cause coughing, wheezing, shortness of breath, irritation of the eyes, ears, nose, throat or lungs, heartbeat changes, or increase your chance of catching a cold. These effects typically last no more than a few hours. We are not aware of any permanent or long-term effects from a short exposure like the one used in this study. The concentration of ozone to which you would be exposed in this study is 300 ppb for 2 hours, which is about the same as spending a few days in a city with poor air quality like Los Angeles, Atlanta or New York City. Air pollution in the outdoor environment is associated with adverse health outcomes, which is why we are doing this study. In susceptible populations like older adults (>65 years of age) or people with cardiac disease, asthma or diabetes, air pollution is associated with increased death rates and increased risk of respiratory and cardiovascular disease. However, this risk in healthy young adults is rare. **You should not engage in heavy levels of exercise for 24 hours before and after the exposure period.**

Supplementation: Infrequently, there is a risk associated with taking fish oil or olive oil supplements. Dietary supplements with fish oil or olive oil are relatively safe as a whole. Allergic reactions to olive oil have been reported, but are rare. High-dose of fish oil may alter blood lipid profile, increase bleeding times and cause stomach upset. Our fish oil and olive oil supplements will be provided by a certified vitamin company and have the same quality as the fish oil and olive oil supplements that you can buy from a vitamin store, grocery store, or pharmacy.

Heart rhythm monitoring: Commonly, preparing your skin for placement of adhesive ECG electrodes and removing the electrodes the next day can cause some temporary redness, irritation, or skin discoloration. Itching or burning occurs infrequently in some people. If this occurs you should call the nursing staff immediately.

Venous blood sampling: The risks associated with taking blood samples are considered minimal. A well-trained member of the staff will draw the blood. It is likely that drawing blood will cause some bruising or minor pain, which usually resolves quickly. Also, a rare complication is skin infection or an infection of the vein in which the blood has been drawn. The risk of getting an infection is minimized by the use of sterile technique. If you do have signs of infection at the site (redness, warmth, painful skin, and swelling) after completion of the procedure, you will need to contact the EPA medical station as soon as possible.

Brachial artery ultrasound: There is little risk associated with ultrasound imaging of the brachial artery, or with brief episodes of forearm ischemia (reduced blood flow). Very commonly, occlusion of blood flow to the arm result in mild discomfort or temporary sensations of tingling or numbness until the blood pressure cuff is released. A small number of patients (about 1 in 200) develop a painless rash on the arm where the blood pressure cuff is placed; this disappears over several days.

Breathing tests (spirometry): You may cough or become dizzy during these tests, but this occurs infrequently. You will be seated in a chair, and if these symptoms occur, they are usually only temporary.

Retinal image: There is negligible risk associated with taking photograph of your retina. The most common side-effect being momentary visual impairment caused by the firing of the flash used by the camera, which resolves within seconds to minutes.

Sputum induction: Multiple testing attempts may cause wheezing in susceptible individuals. A physician is immediately available and rescue albuterol is on hand. You will be carefully monitored with pulmonary function testing to ensure a return to before you leave the research lab. Coughing and on rare occasion, fever or infection has been associated with induced sputum collection.

Exercise: You may experience side effects of exercise including occasional muscle soreness, cramps, or general fatigue. The chances are infrequent to very common depending on your fitness level. These effects are temporary and not typically harmful to subjects. It is also possible that exercise might uncover a previously unidentified pre-existing heart problem that could affect your health.

In addition, there may be uncommon or previously unrecognized risks that might occur. If you do notice any unusual symptoms occurring during the study you should call the EPA medical station 919-966-6232.

What if we learn about new findings or information during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

How will your privacy be protected?

You will be given a study code number. All electronic documents will only have that number. The paper records that the coordinators and medical doctors use may have your name. Your information can be linked to your personal information by the study number, however only study personnel have access to your personal information. Paper records that use your name are kept in a locked file cabinet in the EPA Medical Station of the Human Studies Facility. The Medical Station is locked when not attended by study staff, and the EPA Human Studies Facility has limited access to authorized individuals only, 24 hours/day for 7 days/week. Blood samples will be stored at the EPA Human Studies Facility.

Research studies may be done at many places at the same time. Your personal identifying information will not be sent to outside researchers.

No subjects will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, EPA will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

What will happen if you are injured by this research?

All forms of medical research, diagnosis, and treatment involve some risk of injury or illness. Despite our high level of precaution, you may develop an injury or illness due to participating in this study. If such problems occur, we have physicians and nurses in the building at all times who will provide emergency care as needed. They may also refer you to a local health care facility. In addition, we will contact you within one month to see how you are doing.

If you develop an injury or illness determined by the on-duty physician to be due to your participation in this research, the EPA will reimburse your medical expenses to treat the injury or illness up to $5000. If you believe your injury or illness was due to a lack of reasonable care or other negligent action, you have the right to pursue legal remedy. The Federal Tort Claims Act, 28 U.S.C. 2671 et. seq., provides for money damages against the United Sates when personal injury or property loss results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study?

The total compensation for completion of the study will be $1675. This amount reflects both the procedures or tests involved, and the time required to participate. If you are unable to complete the study for voluntary reasons or failure to comply with eligibility requirements you will receive full compensation for your participation up to that point.

We anticipate performing several tests on you during the course of this study. However, circumstances beyond our control may arise (i.e., equipment failure) which may prevent us from performing a specific test on you. If we are unable to perform a specific test on you which is a primary endpoint for us, you will be compensated for all tests and time completed on that day and rescheduled. If this test is a secondary endpoint for us and is also a source of compensation, you will be paid for that test, but not rescheduled to make up the procedure. Please note that you

will receive an on-time bonus only if you check-in to the medical station on time on both exposure days and the follow-up visit.

In addition, you will be reimbursed for reasonable travel expenses and for parking costs while at the research facility. Money received by participants in research studies is normally treated as ordinary income by taxing authorities and we will report payments made to you to the Internal Revenue Service as required by law. Payments totaling more than $600 in a year from a single or multiple EPA studies will be reported to the IRS. This summary is to emphasize the importance of all the visits, and to signify the importance of your time and commitment to the research study. The following table details the expected compensation for completion of the entire study:

Training day (approximately 4 hours) $150

- Informed consent
- Blood draw
- Pulmonary function test
- Exercise training
- Induced sputum
- Dietary counseling
- Get supplement pills and instructions

Each exposure series

Exposure day 1 (approximately 9 hours) $400

- Blood draws (2X)
- Heart rhythm monitoring (2X)
- Brachial artery ultrasound (2X)
- Retinal image (2X)
- Pulmonary function test (2X)
- Lunch
- Induced sputum $100

Exposure day 2 (approximately 9 hours) $400

- Blood draws (2X)
- Heart rhythm monitoring (2X)
- Brachial artery ultrasound (2X)
- Retinal image (2X)
- Pulmonary function test (2X)
- Lunch
- Induced sputum $100

Follow up day (approximately 3 hours) $200

- Blood draw
- Heart rhythm monitoring
- Brachial artery ultrasound

- Retinal image
- Pulmonary function test

Study on-time bonus $75

Dietary compliance/Study completion $250

- Food frequency questionnaire/counseling
- 3-days food record (3X)
- 6-weeks dietary restriction and 4-weeks dietary supplementation
- Study completion

Total payment = $1675 or ($1475 if you opted out of induced sputum on exposure days)

If you are terminated from the study or chooses to withdraw, you will be reimbursed for time and procedures completed up to that time point. You will receive the study on-time bonus if you check-in to the medical station on time on both exposure days and the follow-up visit.

You should understand that your participation is voluntary. You may terminate your participation in the study at any time without penalty. If you voluntarily elect to withdraw from the study at any time or you fail to maintain compliance with eligibility requirements, you will be paid for that portion of the study that has been completed. In the event a scheduled study activity must be cancelled by the investigators with less than 72 hours prior notice, you will be paid $12 per hour for the time scheduled and canceled. You will be paid in full for any procedures that may have been started during the current visit. Cancellations could occur due to adverse weather conditions, equipment failure, and other unforeseen events. When feasible, canceled visits will be rescheduled.

The investigators also have the right to stop your participation in the study at any time. This could be because you have had an unexpected reaction, have failed to follow instructions, or because the entire study has been stopped, or for some other reason. If you are dismissed by the investigators prior to completion, you will be paid for the entire study excluding the completion bonus.

Will it cost you anything to be in this study?

There will be no cost to you for participating in the study. However, if you are deemed not eligible to participate in the study for medical reasons, we may suggest that you seek follow-up care from your own health care provider for abnormalities discovered during the screening history, physical examination, or the study. Such care is entirely at your own expense. EPA will not provide reimbursement for any follow-up care.

All study procedures will be paid for by the study. We will give you parking coupons to cover the cost of parking. If you live beyond Chapel Hill/Carrboro you will be reimbursed for mileage at the US Government mileage rate in effect at the time.

What if you are a UNC student?
You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?
Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

Who is sponsoring this study?
This research is funded by the U.S. Environmental Protection Agency. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have further questions regarding this study, you should call one of the listed investigators on the first page of this form.

If you feel a research-related injury has occurred, please contact the HSF medical station or one of the investigators listed above. In addition, you should contact the Human Studies Division Human Research Officer and Director of the National Health Effects and Environmental Research Laboratory Human Research Protocol Office at 919-966-6217.

What if you have questions about your rights as a research subject?
All research on human subjects is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously, if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_ subjects@unc.edu and/or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

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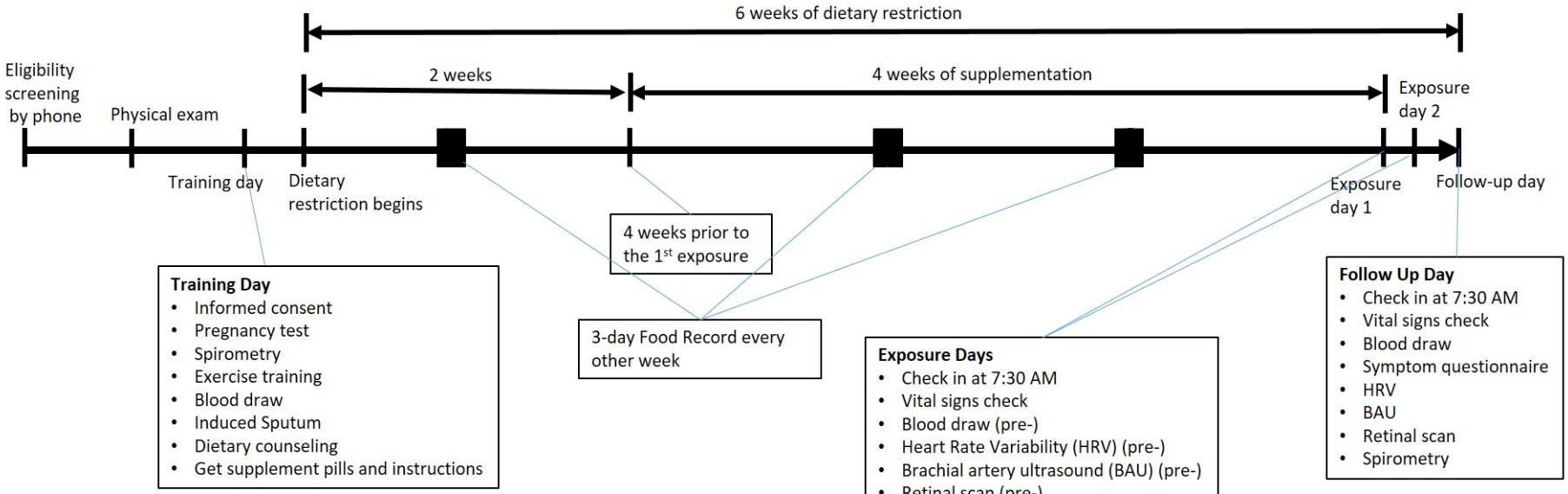

OMEGOZ

Version October 19, 2017

IRB Study # 15-2960
Title of Study: Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects

Principal Investigator: James Samet, PhD, MPH

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily **AGREE** to participate in this research study.

_____ _____
Signature of Research Subject Date

_____
Printed Name of Research Subject

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent

University of North Carolina at Chapel Hill
Consent for Genotyping <u>With</u> Identifying Information

OMG 3

IRB Study # 15-2960
Consent Form Version Date: March 5th, 2018

Title of Study: Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects
Principal Investigator: James Samet, PhD, MPH
Co-Principal Investigators: Haiyan Tong, MD, PhD; Wan Shen, PhD, RD, LDN; Neil Alexis, PhD.
UNC-Chapel Hill Department: US Environmental Protection Agency
UNC-Chapel Hill Phone number(s): (919) 966-0665, (919) 966-4993, (919) 843-9228
Principal Investigator Email Address: samet.james@epa.gov
Funding Source: US Environmental Protection Agency Intramural Federal Research
Study Contact telephone number(s): (919) 966-0665, (919) 966-4993, (919) 843-9228, (919) 966-6211
Study Contact email: samet.james@epa.gov; tong.haiyan@epa.gov; shen.wan@epa.gov; case.martin@epa.gov

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<u>What are some general things you should know about this research study?</u>
Research studies are designed to gain scientific information that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Research with blood, tissue and/or body fluids (specimens) can help researchers understand how the human body works. Research using specimens can also answer other questions. Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat diseases. In the future, some research may help to develop new products, such as drugs.

You may refuse to allow us to have or store your specimen. If you are a patient with an illness, you do not have to be in the research study in order to receive treatment.

Details are discussed below. It is important that you understand this information so that you can make an informed choice. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

<u>What is the purpose of this study?</u>
Recent reports have shown that people with a particular gene, known as the GSTM1 null gene, are more susceptible to air pollutants. The main purpose of this research study is to determine whether fish oil or olive oil supplements can modulate the cardiovascular (heart and blood vessels) and pulmonary (lungs) effects to ozone exposure, a common air pollutant in urban

environments. The purpose of the genotyping is to determine whether you carry a GSTM1 sufficient gene or GSTM1 null gene. Your participation to this genotyping test will not affect your eligibility to participate in this research study.

How many subjects will participate in this study?
If you decide to participate, you will be one of approximately 60 participants in this study.

What will happen if you participate in this study?
We will briefly review your medical history and any medical conditions that you have or medications that you are currently taking. You will sign 2 copies of the study consent form. We will measure your blood pressure and draw up to 60 ml of blood for blood analysis for the main study. With your permission, a portion of your blood sample (about 5 ml) from the collection for the main study will be used for genotyping.

If you have been genotyped before, there will be no genotyping this time.

How will the blood sample be collected?
You will have up to 60 ml (about 4 tablespoons) of blood taken by a registered nurse or other qualified study team member for the main study. With your permission, a portion of the blood (about 5 ml) will be used for genotyping.

What will happen to the blood?
With your permission, a portion of the blood sample (about 5 ml) from the collection for the main study will be used to look at the GSTM1 gene. With your permission, if there are excess samples left over after use for the purposes of this specific study, they will be stored at the U.S. Environmental Protection Agency Human Studies Facility located in Chapel Hill North Carolina. Only project members of the study will have access to the samples.

During the course of this research, other researchers may request access to specimens for as-of-yet unspecified research that may or may not be related to the original research from which the specimens were derived. In these cases, provided appropriate IRB approved consent has been obtained from subjects, these specimens will be provided without identifiers to these other researchers by employing a data use agreement.

Are there any reasons you should not participate?

- You should not participate in this portion of the study if you are not a candidate for the subsequent portions. The inclusion and exclusion criteria will be described. Briefly, you should not have chronic diseases including allergies, lung diseases, diabetes, need for a heart pacemaker, a previous chest pain and heart attack or coronary bypass surgery and uncontrolled high blood pressure. You are on doctor's orders to take fish oil that we do not want to interfere with your therapy. You are currently taking β-blockers (such as atenolol, metoprolol, propanolol, acebutolol). You are currently smoking or have a smoking history within 1 year of the study (defined as more than one pack of cigarettes in the past year) or have a greater than/equal to a 5 pack year smoking history. The investigators and medical stuff will explain other potential exclusionary conditions in detail to you.

What are the possible benefits to you?
There are no direct benefits to you for completing this portion of the study. However, you will know your genotype of GSTM1 gene.

What are the possible risks or discomforts involved with being in this study?
This study might involve the following minimal risks and/or discomforts to you:

1. The risks associated with taking blood samples are considered minimal. A registered nurse or other qualified study team member will draw the blood. It is likely that drawing blood will cause some bruising or minor pain, which usually resolves quickly. Also, a rare complication is skin infection or an infection of the vein in which the blood has been drawn. The risk of getting an infection is minimized by the use of sterile technique. If you do have signs of infection at the site (redness, warmth, painful skin, and swelling) after completion of the procedure, you will need to contact the EPA medical station.

2. Risk of breach of confidentiality is minimal. You will be assigned a study number which will be used for data – not your name. The study number is all that will be entered into computer databases. All paper files which may contain your name or screening number are secure in the EPA building which has limited access 24 hours/day. A numeric coding system will be used to ensure that you cannot be directly identified from the samples alone.

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers

Will there be any cost to you to participate?
The U.S. EPA will pay the costs of this research. You will not be billed for any procedures.

Will you receive anything for being in this study?
You will be paid for participation in the main study. There is no extra compensation for this procedure. We will give you parking coupons to cover the cost of parking. If you live more than 30 miles outside of the Chapel Hill/Carrboro area, you will be reimbursed for mileage at the current government rate.

Who owns the blood samples?
Any blood samples obtained for the purpose of this study become the exclusive property of The U.S. Environmental Protection Agency. The researchers may retain, preserve or dispose of these specimens and may use these specimens for research that may result in commercial applications. There are no plans to compensate you for any future commercial use of these specimens.

How will your privacy be protected?
You will be given a study code number. All electronic documents will only have that number. The paper records that the coordinators and medical doctors use may have your name. Your information can be linked to your personal information by the study number, however only study personnel have access to your personal information. Paper records which use your name are kept in a locked file cabinet in the EPA Medical Station of the Human Studies Facility. The Medical

Station is locked when not attended by study staff, and the EPA Human Studies Facility has limited access to authorized individuals only, 24 hours/day for 7 days/week. Samples used for genetic analysis will be stored at the EPA Human Studies Facility.

Research studies may be done at many places at the same time. Your personal identifying information will not be sent to outside researchers.

No one will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

Will researchers seek approval from you to do future studies involving the blood samples?
By signing this consent form, you are giving your permission for researchers to use your specimens as described above. Current and future research is overseen by a committee called the Institutional Review Board (IRB). The role of the IRB is to protect the rights and welfare of research participants.

In some cases, the IRB may require that you be re-contacted and asked for your consent to use your specimens in a specific research study. You have the right, at that future time, not to participate in any research study for which your consent is sought. Refusal to participate will not affect your medical care or result in loss of benefits to which you are entitled.

Will you receive study results of future research involving your blood samples?
Most research with your specimens is not expected to yield new information that would be meaningful to share with you individually. In rare cases, you may be offered the opportunity to receive information about the results of research in which the specimens were used (for example, findings that would affect your medical care).

Can you withdraw the blood samples from the research study?
If you decide that you no longer wish for the specimens to be stored, you should contact the researchers on the front page of this form. You may also contact the Institutional Review Board, University of North Carolina at Chapel Hill, 919-966-3113, Medical School Building 52, CB 7097, Chapel Hill, NC 27599, or by email at IRB_subjects@unc.edu. It is best to make your request in writing.

Any analysis in progress at the time of your request or already performed prior to your request being received by the researcher will continue to be used as part of the research study. Once the researchers have been notified, your specimens would be destroyed. If you do not make such a request, the specimens may be stored forever. The researchers may choose to destroy the specimens at any time.

What will happen if you are injured by this research?
All forms of medical research, diagnosis, and treatment involve some risk of injury or illness. Despite our high level of precaution, you may develop an injury or illness due to participating in this study. If you develop an injury or illness determined by the on duty physician to be due to your participation in this research, the EPA will reimburse your medical expenses to treat the injury or illness up to $5000. If you believe your injury or illness was due to a lack of reasonable care or other negligent action, you have the right to pursue legal remedy. The Federal Tort Claims Act, 28 U.S.C. 2671 et. seq., provides for money damages against the United Sates when personal injury or property loss results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence.

If a research related injury or illness occurs, you should contact the Director of the EPA NHEERL Human Research Protocol Office at 919.966.6217.

Who is sponsoring this study?
This research is funded by The U.S. Environmental Protection Agency. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have questions, you should contact the researchers listed on the first page of this form or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

What if you have questions about your rights as a research subject?
All research on human subjects is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously, if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_ subjects@unc.edu and/or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

Genetic Information Nondiscrimination Act Guidance
Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

IRB Study # 15-2960
Title of Study: Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects

Principal Investigator: James Samet, PhD, MPH

Subject's Agreement:

I have read the information provided above in the Genotyping with Identifying Information form for IRB study # 15-2960. I have asked all the questions I have at this time.

☐ I **AGREE** to my specimen(s) being used for genotyping with the identifying code(s).

☐ I **DO NOT AGREE** to my specimen(s) being used for genotyping with the identifying code(s).

_____ _____
Signature of Research Participant Date

_____
Printed Name of Research Participant

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent

University of North Carolina at Chapel Hill
Consent for Storing Biological Specimens With Identifying Information

OMG 4

IRB Study # 15-2960
Consent Form Version Date: March 5th, 2018

Title of Study: Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects
Principal Investigator: James Samet, PhD, MPH
Co-Principal Investigators: Haiyan Tong, MD, PhD; Wan Shen, PhD, RD, LDN; Neil Alexis, PhD.
UNC-Chapel Hill Department: US Environmental Protection Agency
UNC-Chapel Hill Phone number(s): (919) 966-0665, (919) 966-4993, (919) 843-9228
Principal Investigator Email Address: samet.james@epa.gov
Funding Source: US Environmental Protection Agency Intramural Federal Research
Study Contact telephone number(s): (919) 966-0665, (919) 966-4993, (919) 843-9228, (919) 966-6211
Study Contact email(s): samet.james@epa.gov; tong.haiyan@epa.gov; shen.wan@epa.gov**; case.martin@epa.gov**

What are some general things you should know about this research study?
Research studies are designed to gain scientific information that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Research with blood, tissue and/or body fluids (specimens) can help researchers understand how the human body works. Research using specimens can also answer other questions. Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat diseases. In the future, some research may help develop new products, such as drugs.

You may refuse to allow us to have or store your specimen. If you are a patient with an illness, you do not have to be in the research study in order to receive treatment.

Details are discussed below. It is important that you understand this information so that you can make an informed choice. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
Air pollution exposure has been found to cause a range of lung and systemic changes in normal subjects. We will be collecting blood samples which will help us to further study this condition. In order to do so, we will need to collect and store blood. Blood samples will be collected in order to look for but not limited to indicators of inflammation due to the Air pollution exposure.

All samples will be stored where only project members will have access to the samples. There is a need to store samples in such a repository because this will be an ongoing study where samples from subjects will be collected over an extended period of time. Storing of samples allows for all samples to be processed at the same time and also allows our scientist the opportunity to further study these samples with as yet unknown questions and techniques.

How will the specimen be collected?
The description of the samples to be collected and the manner in which this will be done have been described in the main study consent.

What will happen to the specimen?
Blood samples will be collected in order to look at but not limited to, indicators of inflammation due to the Air pollution exposure. If there are excess samples left over after use for the purposes of this specific study, they will be stored at the U.S. Environmental Protection Agency Human Studies Facility located in Chapel Hill North Carolina. Only project members of the study will have access to the samples.

During the course of this research, other researchers may request access to specimens (or data) for as-of-yet unspecified research that may or may not be related to the original research from which the specimens were derived. In these cases, provided appropriate IRB approved consent has been obtained form subjects, these specimens (or data) will be provided without identifiers to these other researchers by employing a data use agreement.

What are the possible benefits to you?
You will not benefit directly from being in this research study. This is not a substitute for a routine doctor visit.

This research is designed to benefit society by gaining new knowledge. Given that every member of American society is currently exposed to these pollutants, this study has the potential to contribute to devising effective strategies aimed at protecting millions from the untoward effects of these pollutants.

What are the possible risks or discomforts involved with being in this study?
This study might involve the following risks and/or discomforts to you:

1. Blood sampling will be performed by medical personnel, and entails only a risk of mild discomfort with the infrequent possibility of lightheadedness, fainting, infection or developing a bruise.

2. Risk of breach of confidentiality is minimal. You will be assigned a study number which will be used for data – not your name. The study number is all that will be entered into computer databases. All paper files which may contain your name or screening number are secure in the EPA building which has limited access 24 hours/day. A numeric coding system will be used to ensure that you cannot be directly identified from the samples alone.

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers

Will there be any cost to you for storage of the specimens?
There will be no cost to you for the storage and use of the specimens for research purposes.

Will you receive anything for being in this study?
You will not receive anything for taking part in this study with regard to storage of excess specimens. Reimbursement for participation in the main study is addressed in the detailed consent for that study.

Who owns the specimens?
Any blood, body fluids, or tissue specimens obtained for the purpose of this study become the exclusive property of The U.S. Environmental Protection Agency. The researchers may retain, preserve or dispose of these specimens and may use these specimens for research that may result in commercial applications. There are no plans to compensate you for any future commercial use of these specimens.

How will your privacy be protected?
You will be given a study code number. All electronic documents will only have that number. The paper records that the coordinators and medical doctors use may have your name. Your information can be linked to your personal information by the study number, however only study personnel have access to your personal information. Paper records which use your name are kept in a locked file cabinet in the EPA Medical Station of the Human Studies Facility. The Medical Station is locked when not attended by study staff, and the EPA Human Studies Facility has limited access to authorized individuals only, 24 hours/day for 7 days/week. Samples used for genetic analysis will be stored at the EPA Human Studies Facility.

Research studies may be done at many places at the same time. Your personal identifying information will not be sent to outside researchers.

No one will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

Will researchers seek approval from you to do future studies involving the specimens?
By signing this consent form, you are giving your permission for researchers to use your specimens as described above. Current and future research is overseen by a committee called the Institutional Review Board (IRB). The role of the IRB is to protect the rights and welfare of research participants.

In some cases, the IRB may require that you be re-contacted and asked for your consent to use your specimens in a specific research study. You have the right, at that future time, not to participate in any research study for which your consent is sought. Refusal to participate will not affect your medical care or result in loss of benefits to which you are entitled.

Will you receive study results of future research involving your specimens?
Most research with your specimens is not expected to yield new information that would be meaningful to share with you individually. In rare cases, you may be offered the opportunity to receive information about the results of research in which the specimens were used (for example, findings that would affect your medical care).

Can you withdraw the specimens from the research study?
If you decide that you no longer wish for the specimens to be stored, you should contact the researchers on the front page of this form. You may also contact the Institutional Review Board, University of North Carolina at Chapel Hill, 919-966-3113, Medical School Building 52, CB 7097, Chapel Hill, NC 27599, or by email at IRB_subjects@unc.edu. It is best to make your request in writing.

Any analysis in progress at the time of your request or already performed prior to your request being received by the researcher will continue to be used as part of the research study. Once the researchers have been notified, your specimens would be destroyed. If you do not make such a request, the specimens may be stored forever. The researchers may choose to destroy the specimens at any time.

What will happen if you are injured by this research?
All forms of medical research, diagnosis, and treatment involve some risk of injury or illness. Despite our high level of precaution, you may develop an injury or illness due to participating in this study. If you develop an injury or illness determined by the on duty physician to be due to your participation in this research, the EPA will reimburse your medical expenses to treat the injury or illness up to $5000. If you believe your injury or illness was due to a lack of reasonable care or other negligent action, you have the right to pursue legal remedy. The Federal Tort Claims Act, 28 U.S.C. 2671 et. seq., provides for money damages against the United Sates when personal injury or property loss results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence.

If a research related injury or illness occurs, you should contact the Director of the EPA NHEERL Human Research Protocol Office at 919-966-6217.

Who is sponsoring this study?
This research is funded by The U.S. Environmental Protection Agency. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, you should contact the researchers listed on the first page of this form or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

What if you have questions about your rights as a research subject?

All research on human subjects is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously, if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_ subjects@unc.edu and/or the EPA Director of the National Health and Environmental Effects Human Research Laboratory Protocol Office at 919-966-6217.

IRB Study # 15-2960
Title of Study: Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects

Principal Investigator: James Samet, PhD, MPH

Subject's Agreement:
I have read the information provided above in the Storing Biological Specimens with Identifying Information form for IRB study # 15-2960. I have asked all the questions I have at this time.

☐ I **AGREE** to my specimen(s) being stored with the identifying code(s).

☐ I **DO NOT AGREE** to my specimen(s) being stored with the identifying code(s).

_____ _____
Signature of Research Participant Date

_____
Printed Name of Research Participant

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent

University of North Carolina at Chapel Hill
Consent to Re-Contact Following Removal From the Study
Re-contact Consent

OMG 5

IRB Study # 15-2960
Consent Form Version Date: March 5th, 2018

Title of Study: Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects
Principal Investigator: James Samet, PhD, MPH
Co-Principal Investigators: Haiyan Tong, MD, PhD; Wan Shen, PhD, RD, LDN; Neil Alexis, PhD.
UNC-Chapel Hill Department: US Environmental Protection Agency
UNC-Chapel Hill Phone number(s): (919) 966-0665, (919) 966-4993, (919) 843-9228
Principal Investigator Email Address: samet.james@epa.gov
Funding Source: US Environmental Protection Agency Intramural Federal Research
Study Contact telephone number(s): (919) 966-0665, (919) 966-4993, (919) 843-9228, (919) 966-6211
Study Contact email(s): samet.james@epa.gov; tong.haiyan@epa.gov; shen.wan@epa.gov; case.martin@epa.gov

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You have previously given consent to participate in this study. As an added measure to protect your safety, we would like to have your permission to contact you to follow-up on your health if you are removed from the study for safety/medical reasons. If you are removed from the study for safety/medical reasons, then a member of the study team will contact you within 30 days of your removal from the study to follow-up on the concern that led to your removal from the study.

The purpose of this form is to gain your permission to contact you after your removal from the study if you are removed for safety/medical reasons. By signing this form you acknowledge that you have read this form in its entirety and a member of the study team has explained the change in the study protocol. You also acknowledge that all of the terms of any consent forms that you have previously signed regarding this study still apply.

IRB Study # 15-2960
Title of Study: Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects

Principal Investigator: James Samet, PhD, MPH

Participant's Agreement:

I have read the information provided above in the Re-contact form for IRB study # 15-2960. I have asked all the questions I have at this time.

☐ I **AGREE** to be contacted by a study team member within 30 days of my removal from the study if I am removed for safety/medical reasons.

☐ I **DO NOT AGREE** to be contacted by a study team member within 30 days of my removal from the study if I am removed for safety/medical reasons.

_____ _____
Signature of Research Participant Date

_____
Printed Name of Research Participant

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent

OMG
6

University of North Carolina at Chapel Hill
Consent for Storing Biological Specimens With Identifying Information

IRB Study #05-2528 (formerly 05-PED-1073)

Consent Form Version Date: June 11, 2013

Title of Study: Center for Environmental Medicine, Asthma and Lung Biology Repository for Storage of Coded Samples

Principal Investigator: Neil Alexis, PhD
UNC-Chapel Hill Department: Pediatrics/Center for Environmental Medicine, Asthma and Lung Biology
UNC-Chapel Hill Phone number: 919-966-9915

Study Contact telephone number: 919-966-0759
Study Contact email: martha_almond@med.unc.edu

What are some general things you should know about this research study?
Research studies are designed to gain scientific information that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Research with blood, tissue and/or body fluids (specimens) can help researchers understand how the human body works. Research using specimens can also answer other questions. Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat diseases. In the future, some research may help to develop new products, such as drugs.

You may refuse to allow us to have or store your specimen. If you are a patient with an illness, you do not have to be in the research study in order to receive treatment.

Details are discussed below. It is important that you understand this information so that you can make an informed choice. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
The purpose of the Center for Environmental Medicine, Asthma and Lung Biology (CEMALB) repository is to provide a centralized location for storage of excess samples collected as part of other studies which are then coded and saved for future research. Researchers in the future may want access to these samples to study questions related to human health and the effect of various agents on humans as well as for future currently undesignated studies including possible genetic research. Samples to be stored in the repository may include specimens such as blood, tissue, body fluids, and sputum samples.

How will the specimen be collected?
Specimens that will be saved in the repository will be collected as part of a particular study for which you have already provided your consent. The description of the samples to be collected and the manner in which this will be done have been described in the main study consent.

What will happen to the specimen?
Specimens that are left over after the specific analyses for the main study are completed will be stored indefinitely in a refrigerator or -80 degree C freezer or as slides in the CEMALB. These samples will be coded so that future investigators will not have your personal identifying information when they decide to use the samples for new studies. Any information which would link your samples to personal identifying information is protected as part of an Honest Broker system. This means the linking information is kept by study coordinators who act as honest brokers and who will not, under any circumstances, release any information to future investigators that would link your samples to personal identifying information. Future researchers may want to study samples from healthy control subjects or they may want to do analyses on samples from subjects with health concerns such as asthma. Alternatively, researchers may want samples from subjects with specific non-identifying demographic or clinical characteristics. The code number on the stored specimens allows the coordinators to direct the researcher to the repository samples needed for their specific research questions without divulging any personal identifying information.

What are the possible benefits to you?
Benefits to you are unlikely. These studies (current and future) may provide additional information that will be helpful in understanding research questions such as those related to health, inflammation, and response to air pollution.

What are the possible risks or discomforts involved with being in this study?
There are no known risks to you although there may be risks that, at this time, are unknown.

Will there be any cost to you for storage of the specimens?
There will be no cost to you for the storage and use of the specimens for research purposes.

Will you receive anything for being in this study?
You will not receive anything for allowing us to store your excess samples after they are used for the purposes of the main study. You will be reimbursed for participation in the main study as outlined in the main study consent form.

Who owns the specimens?
Any blood, body fluids, or tissue specimens obtained for the purpose of this study become the exclusive property of CEMALB. The researchers may retain, preserve or dispose of these specimens and may use these specimens for research that may result in commercial applications. There are no plans to compensate you for any future commercial use of these specimens.

How will your privacy be protected?
Your identifiable data will be kept by the study coordinators and future investigators who wish to use your coded samples will not have access to this data. Offices for storage of your identifiable

data are locked when coordinators are not in attendance, and the coordinators will not, under any circumstances, provide this information to future researchers. The coded specimens may be shared other outside research groups, both within the University of North Carolina System, or without (such as the Environmental Protection Agency with whom we often collaborate). Research studies may be done at many places at the same time. Your personal identifying information will not be sent to outside researchers.

No one will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

A Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

Will researchers seek approval from you to do future studies involving the specimens?
By signing this consent form, you are giving your permission for researchers to use your specimens as described above. Current and future research is overseen by a committee called the Institutional Review Board (IRB). The role of the IRB is to protect the rights and welfare of research participants.

In some cases, the IRB may require that you be re-contacted and asked for your consent to use your specimens in a specific research study. You have the right, at that future time, not to participate in any research study for which your consent is sought. Refusal to participate will not affect your medical care or result in loss of benefits to which you are entitled.

Will you receive study results of future research involving your specimens?
Most research with your specimens is not expected to yield new information that would be meaningful to share with you individually. In rare cases, you may be offered the opportunity to receive information about the results of research in which the specimens were used (for example, findings that would affect your medical care).

Can you withdraw the specimens from the research study?
If you decide that you no longer wish for the specimens to be stored, you should contact the researchers on the front page of this form. You may also contact the Institutional Review Board, University of North Carolina at Chapel Hill, 919-966-3113, Medical School Building 52, CB 7097, Chapel Hill, NC 27599, or by email at IRB_subjects@unc.edu. It is best to make your request in writing.

Any analysis in progress at the time of your request or already performed prior to your request being received by the researcher will continue to be used as part of the research study. Once the researchers have been notified, your specimens would be destroyed. If you do not make such a request, the specimens may be stored forever. The researchers may choose to destroy the specimens at any time.

Who is sponsoring this study?
Funding for the repository for your excess samples is provided by CEMALB

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have questions, you should contact the researchers listed on the first page of this form.

What if you have questions about your rights as a research subject?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously, if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_ subjects@unc.edu.

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate. I agree to my specimen(s) being stored with the identifying code(s).

_____ _____
Signature of Research Subject Date

_____
Printed Name of Research Subject

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent

University of North Carolina at Chapel Hill
Consent Checklist

OMG
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IRB Study # 15-2960
Consent Form Version Date: March 5th, 2018

Title of Study: Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects
Principal Investigator: James Samet, PhD, MPH
Co-Principal Investigators: Haiyan Tong, MD, PhD; Wan Shen, PhD, RD, LDN; Neil Alexis, PhD.
UNC-Chapel Hill Department: US Environmental Protection Agency
UNC-Chapel Hill Phone number(s): (919) 966-0665, (919) 966-4993, (919) 843-9228
Principal Investigator Email Address: samet.james@epa.gov
Funding Source: US Environmental Protection Agency Intramural Federal Research
Study Contact telephone number(s): (919) 966-0665, (919) 966-4993, (919) 843-9228, (919) 966-6211
Study Contact email(s): samet.james@epa.gov; tong.haiyan@epa.gov; shen.wan@epa.gov; case.martin@epa.gov

_____ I have read all the consent forms (forms OMG-1 to OMG-6) for the study titled "*Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects*".

_____ A member of the study team has reviewed the consent form titled, "*Consent to Participate in a Research Study*" for the study titled, "*Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects*" with me.

_____ I was given the opportunity to ask a member of the study team questions about the study and my involvement in the study.

_____ I have been made aware that the purpose of this research study is to determine whether fish oil or olive oil supplements can affect the cardiovascular (heart and blood vessels) and pulmonary (lungs) effects of ozone exposure, a common air pollutant in urban environments.

_____ I understand that there are risks associated with my participation in this study. A study team member has discussed with me potential risks associated with participation in this study, and the measures that will be taken by the study team to reduce risk.

_____ A member of the study team has discussed genotyping with me and I have been given the opportunity to either opt-in or opt-out of being genotyped as a part of this study.

_____ I understand that I have the ability to terminate my involvement in the study at any time for any reason and that I am under no obligation to complete the study.

_____ A member of the study team has reviewed the form, "*Consent for Storing Biological Specimens with Identifying Information*" with me and explained how, with my consent, blood samples and sputum samples taken from me during the course of this study will be stored.

_____ I understand that I can submit a written request at any time, during or after the completion of this study, to the Principle Investigator asking for my specimens to be destroyed.

_____ I have been made aware that if I choose to end my involvement in the study prior to completion of my study-related visits/activities, I will receive compensation at 100% of the indicated rate up to that point that I participated in the study.

_____ I have been given contact information for the Principal Investigator and the Medical Station at the EPA Human Studies Facility.

_____ I understand that I can ask a member of the study team or the medical staff a question regarding the study and my involvement in the study at any time.

_____ I have had an opportunity to ask a member of the study team any questions that I have up to this point regarding the study and my involvement in the study.

_____

IRB Study # 15-2960
Title of study: Efficacy of Fish Oil or Olive Oil Supplementation on the Health Effects of Ozone Exposure in Healthy Young Subjects.

Principal investigator: James Samet, PhD, MPH.

Subject's Agreement:

I verify that, to the best of my knowledge and belief, all of the information contained in the consent form was read and understood by me prior to signing it. I further certify that I have read the information above and by initialing at each statement and signing below I acknowledge that I agree and understand each statement above. I have asked all the questions I have at this time.

_____ _____
Signature of Research Subject Date

_____
Printed Name of Research Subject

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent